Case Report

Pantoprazole and Perinuclear Antineutrophil Cytoplasmic Antibody-Associated Vasculitis

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ABSTRACT. Systemic vasculitis may, at times, be drug-induced and associated with antineutrophil cytoplasmic antibodies (ANCA). However, pantoprazole, a commonly used and well-tolerated proton pump inhibitor, has not previously been reported to cause ANCA-associated syndromes. We describe a patient who developed interstitial nephritis, cutaneous vasculitis, a perinuclear ANCA staining pattern (pANCA) on immunofluorescence, and anti-myeloperoxidase antibodies (MPO-ANCA) in association with pantoprazole. We review various immune-mediated syndromes reported in association with proton pump inhibitors, including one report of omeprazole associated with interstitial nephritis and the development of ANCA. (J Rheumatol 2006;33:629–32)

Key Indexing Terms:
VASCULITIS PANCA PANTOPRAZOLE PROTON PUMP INHIBITOR

The pathogenesis of systemic vasculitis is complex and may be associated with medication use. Leukotriene inhibitors, antibiotics, antithyroid drugs, and illicit drugs have all been shown to induce systemic vasculitis. Pantoprazole, a medication commonly used for gastroesophageal reflux disease, Zollinger-Ellison syndrome, *Helicobacter pylori* infections, and peptic ulcers, has not been reported to cause vasculitis. Pantoprazole binds irreversibly to the proton pump of gastric mucosal parietal cells and inhibits hydrochloric acid secretion[1]. It is similar to other proton pump inhibitors (PPI), a class of drugs generally regarded as safe. We present the first reported case of pantoprazole-associated vasculitis with antineutrophil cytoplasmic antibodies in a perinuclear staining pattern (pANCA).

CASE REPORT

A 65-year-old woman with a history of panic attacks, abdominal aortic stent placement, and a cholecystectomy was admitted to hospital for acute pancreatitis. While hospitalized, the patient was initiated on pantoprazole. Discharge medications included pantoprazole as well as oxazepam and propranolol, both of which she had taken for over 20 years.

In the weeks following her discharge, the patient developed daily fevers up to 102°F, night sweats, fatigue, and anorexia. She lost 27 pounds over 3 months and reported fullness in her left ear and tinnitus. Laboratory testing revealed new renal failure with pANCA and anti-myeloperoxidase antibody (MPO-ANCA) positivity (see Table 1). Computed tomography with contrast of the chest, abdomen, and pelvis performed after laboratory evaluation revealed no sign of malignancy. One week later, the patient developed a raised erythematous rash on her lower legs that progressed to involve the dorsum of her hands, arms, thighs, abdomen and back within days.

She was admitted to our institution 3 weeks later for rapidly progressive renal failure. The physical examination was notable for fever and +1 pitting edema of the lower extremities with palpable purpura below the knees and macular blanching erythema over the thighs, abdomen, arms, and back. Blood and urine cultures were negative, common causes of vasculitis were excluded, and pANCA and MPO-ANCA were positive once again (see Table 1 for details). Additionally, a transthoracic echocardiogram did not reveal evidence of endocarditis. Methylprednisolone 1 g intravenously daily was initiated. Pantoprazole and propranolol were continued. She became afebrile and the rash began to resolve.

Kidney biopsy revealed acute and chronic granulomatous interstitial nephritis. Of the 8 glomeruli examined, 2 were globally sclerotic, and none displayed evidence of glomerulonephritis. Electron microscopy revealed ischemic injury with wrinkling and collapse of glomerular tufts.

Immunofluorescence demonstrated a pauciimmune pattern. Pantoprazole was discontinued due to suspicion of a drug-induced syndrome. Skin biopsy then revealed lymphocytic vasculitis with focal necrosis, eosinophils, red cell extravasation, edema, and spongiosis of the overlying epidermis consistent with a drug reaction.

Intravenous methylprednisolone was changed to oral prednisone, and hemodialysis was initiated. The rash resolved over several days. The patient was discharged taking prednisone 60 mg daily that was tapered and stopped after one week. Rash and fever returned within one week, and the patient was readmitted. Prednisone was reinitiated and after 3 weeks taking 20 mg daily, her rash resolved, dialysis was discontinued, and pANCA and MPO-ANCA levels continued to decline, eventually becoming negative (see Table 1).

DISCUSSION

Drug-induced vasculitis can present with a wide range of manifestations, most commonly including fever, malaise, eosinophilia, arthralgia/arthritis, palpable purpura or petechiae, and renal involvement including glomerulonephritis or interstitial nephritis[2]. Of the numerous drugs that have been reported to induce vasculitis, the best evidence for an associ-

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Table 1. Pertinent laboratory results. Reference values are given in parentheses.

Laboratory Results	Baseline†	3 months	4 months	5 months	8 months
WBC (4–11 b/l)	11.5	14.1	15.3	10.3	11.0
Eosinophils, % (< 6)	3.5	4	9.4	0.3	
Hgb (12.5–15 g/dl)	13.2	8.1	7.1	12.1	14.0
Plts (140–400 b/l)	300	613	664	241	301
BUN (7–26 mg/dl)	9	66	99	55	48
Cr (0.7–1.4 mg/dl)	1.1	4.8	9	2.5	2.2
UA	Normal	2+ protein 3+ blood RBC 51–100 WBC 0–2 Casts: negative	1+ protein 3+ blood RBC 45 WBC 3 Casts: negative	3+ protein 3+ blood RBC 21–50 WBC 6–10 Casts: negative	
Urine eosinophils			< 1 %		
ESR (< 30 mm/h)			123	15	
CRP (< 0.8 mg/dl)		20.9	26	0.8	
C3 (88–201 mg/dl)			127		
C4 (16–47 mg/dl)			27		
pANCA (negative)		1:640	> 1:640	1:80	Negative
MPO-ANCA (< 20)		114.66	87.98	22.48	
cANCA (negative)		Negative	Negative	Negative	Negative
PR3-ANCA (< 20)		0.4	0.69	0	
Hepatitis B/C serologies (nonreactive)			Nonreactive		Nonreactive
ANA (negative)			Negative		
Cryoglobulins (negative)			Negative		
RPR (nonreactive)			Nonreactive		
ACL IgG (< 15)			< 9.0		
ACL IgM (< 12.5)			10.2		
ß$_2$GPI IgG & IgM (< 20)			< 20		
ACE (9–67)		21			

WBC: white blood cells; Hgb: hemoglobin; plts: platelets; BUN: blood urea nitrogen; Cr: creatinine; UA: urinalysis; RBC: red blood cells; ESR; erythrocyte sedimentation rate; CRP: C-reactive protein; pANCA: perinuclear antineutrophil cytoplasmic antibody; MPO-ANCA: anti-myeloperoxidase antibody; cANCA: cytoplasmic ANCA; PR3-ANCA: antiproteinase 3 antibody; ANA: antinuclear antibody; RPR: rapid plasma reagin; aCl: anticardiolipin antibody; ß$_2$GPI: beta$_2$ glycoprotein I antibody; ACE: angiotensin converting enzyme. † Less than 1 mo prior to exposure.

ation with ANCA is for cases involving propylthiouracil and hydralazine[2]. Most cases report MPO-ANCA rather than antiproteinase 3 antibodies (PR3-ANCA)[2,3]. The interval between the first exposure to a drug and appearance of symptoms varies from hours to years[3]. Treatment is based on withdrawal of the agent with the possible addition of glucocorticoids and cytotoxic agents, as it has been noted that drug discontinuation does not always preclude progression of disease[2].

A review of the literature demonstrates that various immune-mediated syndromes have been reported in association with PPI. Manifestations described after exposure to omeprazole include cutaneous leukocytoclastic vasculitis, hemolytic anemia, polyarthritis, pityriasis rosea, and erythema nodosum (see Table 2). The age of these patients ranged from 27 to 80 years. They were being treated for peptic ulcer disease (n = 5), gastritis/esophagitis (n = 2), and gastroesophageal reflux disease (n = 1). Eight patients (66.7%) manifested skin lesions; of these, 4 were confirmed by biopsy. Five patients (41.7%) had arthralgia or arthritis. The ANCA status of these patients was not reported. Multiple reports of PPI-induced (mainly omeprazole) interstitial nephritis exist; however, currently there exists only one report of a patient taking a PPI developing ANCA-associated interstitial nephritis[12]. Like our patient, the case patient had pANCA positivity and required steroids in addition to drug withdrawal. In contrast, MPO-ANCA testing was not reported, and the patient had no skin involvement (see Table 3 for details).

Although we describe a single case of pantoprazole and ANCA-associated vasculitis, using proposed guidelines[2] we find good evidence for causality. Our patient demonstrated common clinical manifestations of drug-induced vasculitis: palpable purpura, fever, malaise, weight loss, and eosinophilia, with confirmation of interstitial nephritis and cutaneous vasculitis by biopsy. Next, there was a clear temporal association: the syndrome began within a few weeks after initiating pantoprazole treatment. Further, manifestations improved, and pANCA and MPO-ANCA levels became negative with the withdrawal of pantoprazole and continued tapering of prednisone. (In retrospect, the initial prednisone taper was too rapid for the degree of disease manifested and led to flare.) Finally, through a clinical and pathologic investigation, we found no other conditions present that might cause the vasculitis. Although there is one case report of a patient developing leukocytoclastic vasculitis after taking propranolol for 2

Table 2. Prior reports of omeprazole and autoimmune manifestations other than interstitial nephritis.

Patient	Omeprazole Duration	Signs & Symptoms	Pathology	Treatment	Outcome	Reference
Moderate to Strong Evidence of Association						
71-year-old female with PUD	4 weeks	Maculopapular rash	Skin biopsy: LCV	Withdrawal of omeprazole	Skin lesions resolved within few days	4
35-year-old female with GERD and esophageal spasm	NA	Fever, 2+ pitting edema, EN	NA	Withdrawal of all medications incl. omeprazole. Indomethacin initiated Rechallenge with omeprazole Withdrawal of omeprazole	Nodules and edema improved 4 wks later Fever and EN returned in 12 h Symptoms resolved 3 wks later	5
57-year-old male with gastric erosion	2 weeks	Polyarthralgia and EN	NA	Withdrawal of omeprazole	Arthralgia and rash resolved 18 days later	6
NA	2 days	Hemolytic anemia	NA	Withdrawal of omeprazole	hemoglobin normalized	7
80-year-old female with PUD	4–5 days	Truncal rash		Withdrawal of omeprazole	Rash resolved 2 mo later	8
	4 days	Pruritic erythematous scaly plaques	Skin biopsy: pityriasis rosea	Withdrawal of omeprazole Topical steroid initiated	Rash resolved several mo later	
71-year-old male	2 days	Polyarteritis	NA	Withdrawal of omeprazole Rechallenge with omeprazole Withdrawal of omeprazole	Improvement Recurrence Resolution	6
27-year-old female with PUD	10 days	Swelling, pruritis, erythema of fingers, knees and ankles	NA	Withdrawal of omeprazole	Symptoms resolved 10 days later	6
79-year-old female with gastritis	20 days	Intermittent polyarthritis	NA	Withdrawal of omeprazole	Arthritis resolved	6
50-year-old male with esophagitis	3–4 months	IP arthralgia	NA	Withdrawal of omeprazole Rechallenge with omeprazole Withdrawal of omeprazole	Arthralgia rapidly resolved Recurrence Rapid resolution	6
Association Less Likely Due to Other Medication or Underlying Disease						
76-year-old patient on celecoxib 8 days	NA	Purpuric skin lesions	Skin biopsy: LCV	Withdrawal of omeprazole and celecoxib	Lesions regressed 3 weeks later	9
78-year-old male with Crohn's disease, cryptogenic cirrhosis, lower extremity arteritis	2 weeks	Hemorrhagic bullae (Culture positive for coagulase negative *Staphylococcus*)	Skin biopsy: vasculitis	Withdrawal of omeprazole	Blisters resolved 2 weeks later. New purpura developed, readmitted one week later with sepsis, died from DIC	10
63-year-old male with inclusion body myopathy	2 weeks	Fever, arthritis, Raynaud's, pedal edema, positive ANA, antihistone antibody and anticardiolipin IgG	NA	Withdrawal of omeprazole	Residual MCP swelling & mild pedal edema 2 months later. Antihistone antibody negative	11

PUD: peptic ulcer disease; LCV: leukocytoclastic vasculitis; GERD: gastroesophageal reflux disease; NA: not available; EN: erythema nodosum; IP: interphalangeal; DIC: disseminated intravascular coagulation; ANA: antinuclear antibody; MCP: metacarpophalangeal joints.

years[13], resolution in our case has occurred while propranolol and oxazepam have been continued; therefore, these drugs are less likely causes. Definitive diagnosis of pantoprazole-induced pANCA vasculitis could be confirmed only by rechallenge with pantoprazole; given the severity of the patient's disease, rechallenge would be unethical.

It is known that pANCA can be directed towards multiple neutrophilic cytoplasmic antigens. Evidence indicates, however, that pANCA combined with MPO-ANCA is 99% specific for microscopic polyangiitis and idiopathic rapidly progressive glomerulonephritis[14]. The issue remains then as to why patients with drug-induced vasculitis would produce MPO-ANCA as well. This suggests a common mechanism for drug-induced and idiopathic ANCA-associated vasculitides; currently these processes remain unclear. It is clear, however, that a patient such as ours with a clinical syndrome of fever, weight loss, rapidly progressive renal failure, rash, and MPO-ANCA could easily be thought to have an entity such as microscopic polyangiitis and continued on the drug until biopsy results suggest otherwise. In fact, it was not until the renal biopsy revealed the presence of interstitial nephritis and not glomerulonephritis that we began to think of alternate diagnoses, i.e., a drug-induced ANCA syndrome. We submit that a systemic illness such as our patient's should not exclude the consideration of medications as the cause, even those with a good safety profile such as pantoprazole.

Table 3. Patients with proton pump inhibitor-associated ANCA positive interstitial nephritis.

Patient	Symptoms	Pathology	ANCA	Treatment	Outcome	Reference
65-year-old male with esophagitis on omeprazole 4 mo	Fever/chills, anorexia, weight loss, hematuria, proteinuria, elevated creatinine	Renal biopsy: interstitial nephritis	pANCA 1:80	Withdrawal of omeprazole Prednisolone 40 mg po daily initiated 1 week later	Renal function normalized 4 weeks later	4
			pANCA negative		Eventual full recovery of renal function.	
65-year-old female with pancreatitis and aortic vascular disease on pantoprazole 1-2 wks	Fever, fatigue, anorexia, weight loss, hematuria, proteinuria, elevated creatinine & rash	Renal biopsy: interstitial nephritis Skin biopsy: vasculitis	pANCA 1:640 MPO-ANCA 114.66	Withdrawal of pantoprazole. Methylprednisolone 1 g IV × 2 doses then prednisone 60 mg po daily initiated.	Rash improved	Current report
			pANCA 1:160 MPO-ANCA 35.46	Prednisone discontinued after rapid taper	Rash returned	
			pANCA 1:80 MPO-ANCA 22.48	Prednisone reinitiated and slowly tapered to 20 mg po daily	Rash resolved. Renal failure improved	

pANCA: perinuclear antineutrophil cytoplasmic antibody; MPO-ANCA: anti-myeloperoxidase antibody; po: oral; IV: intravenous.

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