

Antineutrophil Cytoplasmic Antibody Vasculitis Associated with Influenza Vaccination

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Key Words

Antineutrophil cytoplasmic antibody · Vasculitis · Influenza immunization

Abstract

Background: Administration of influenza vaccines has been associated with the development of autoantibodies and autoimmune rheumatic disease. **Patients:** We discuss 2 patients who developed antineutrophil cytoplasmic antibody-associated vasculitis (AAV) in temporal association with influenza immunization. AAV was diagnosed 2 and 4 weeks after immunization in these patients. Both patients had renal involvement with one requiring dialysis. Both patients were treated with cyclophosphamide and corticosteroids, and plasmapheresis was added to the immunosuppressive regimen in one patient with dialysis-dependent renal failure. Both patients achieved disease remission. The patient with initial dialysis-dependent renal failure reached end-stage renal disease. There are 6 previous cases of AAV in the literature described in temporal association with administration of influenza vaccines. **Conclusion:** A causal role of vaccines in AAV cannot be confirmed with these case reports. The temporality suggests that the influenza vaccine

may be a triggering factor for induction of vasculitis in predisposed individuals. We review the literature on reported cases of AAV following influenza vaccine administration and discuss possible mechanisms for influenza vaccine-associated AAV.

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Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) includes granulomatosis with polyangiitis (GPA), microscopic polyangiitis and eosinophilic GPA. AAV is a heterogeneous group of disorders prone to cycles of remission and relapses. AAV is characterized by the presence of circulating ANCAs in 90% of the cases [1, 2]. AAV is a rare disease with an annual incidence of only 1 in 20 million [3]. ANCAs are implicated in the pathogenesis of AAV; however, the events leading to the initiation of these vasculitides are obscure. Genetic, environmental and infection-related risk factors have been implicated. Geographic and seasonal differences in the incidence of AAV have also been described. The geographic differences may suggest that differences in genet-

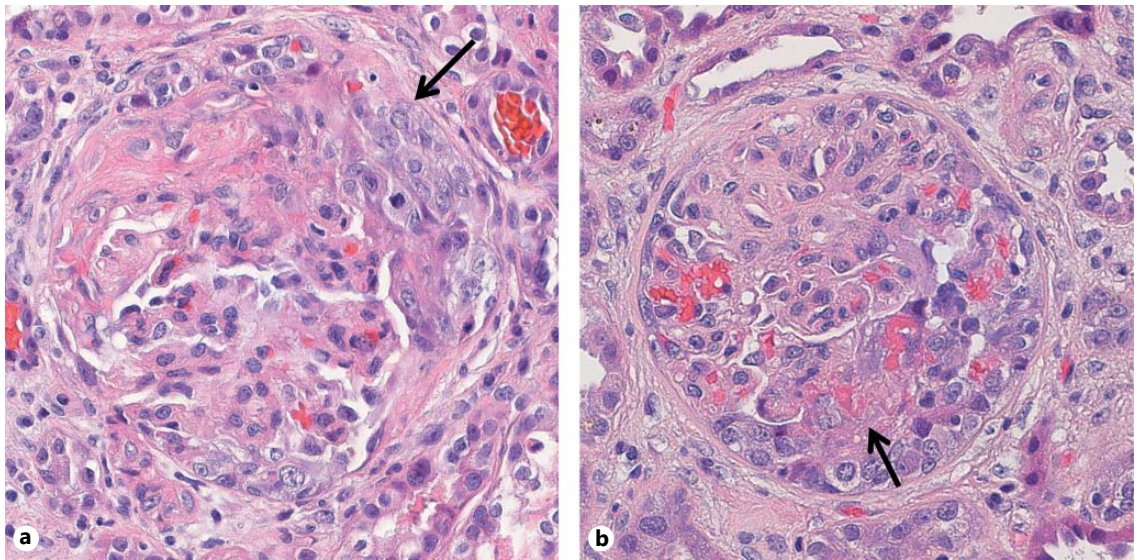


Fig. 1. Renal biopsy from 75-year-old female 4 months after influenza vaccination demonstrating necrotizing and crescentic glomerulonephritis. Numerous glomeruli show cellular crescents (arrow) (a), with fibrin deposition and necrosis (arrow) within a few crescents (b). Original magnification $\times 160$.

ic background or variations in temporal distribution of the initiating agent in different regions may have an etiologic role in AAV, while the seasonal differences in incidence point to an infectious etiology. Furthermore, drugs have been implicated as an initiating factor for AAV [4]. Herein, we present 2 cases of AAV associated with influenza vaccination and present a literature review of cases of AAV that have had a temporal association with influenza vaccination.

Case 1

An active 75-year-old Caucasian female with a past medical history of chronic obstructive pulmonary disease and baseline serum creatinine of 0.7 mg/dl was evaluated for acute kidney injury in January 2013. She developed progressive fatigue and was found to have an elevated serum creatinine of 1.8 mg/dl 4 weeks after an influenza vaccination in September 2012. She complained of epistaxis, nasal crusting, poor appetite and nausea during this period. She underwent esophagogastroduodenoscopy which revealed duodenitis and was placed on omeprazole. Her nausea improved, but she continued with poor appetite and lost 17 pounds. Her blood work in January revealed blood urea nitrogen of 65 mg/dl and serum creatinine of 7.2 mg/dl. Her urinalysis revealed proteinuria and hematuria with red blood cell casts. Her serologies revealed a positive perinuclear ANCA at a titer of 1:320 with a positive myeloperoxidase ELISA at a titer of 78 units. Her antinuclear antibodies and antiglomerular basement membrane antibodies were negative. Her physical

exam was remarkable for conjunctival pallor. Examination of the rest of the systems was unremarkable. Renal biopsy was performed and revealed necrotizing and crescentic pauci-immune glomerulonephritis (fig. 1). She was started on hemodialysis and treated with intravenous methyl prednisone followed by oral prednisone, cyclophosphamide and plasmapheresis. Except for sinus involvement, she did not have any evidence of any other organ involvement. At 3 months after therapy, she was still dialysis dependent.

Case 2

A healthy 50-year-old Caucasian male received the influenza vaccine in October 1997. Two days later he developed fatigue, chills and low-grade fevers. Over the next 4 weeks he experienced worsening joint pains and muscle aches. His physical exam was notable for splinter hemorrhages in his finger nails, but the rest of his exam was unremarkable. Workup at that time demonstrated an erythrocyte sedimentation rate of 56 mm/h, positive rheumatoid factor and positive cytoplasmic ANCA at a titer of 1–80 with a positive proteinase 3 ELISA. Blood cultures were negative. A transthoracic echocardiogram did not reveal any valvular vegetation. Two weeks later, he was noted to have microscopic hematuria and an increase in his serum creatinine from 0.9 to 1.3 mg/dl. Renal biopsy revealed necrotizing vasculitis and focal necrotizing pauci-immune glomerulonephritis. CT chest was unremarkable. He was treated with oral prednisone and oral cyclophosphamide; after achievement of remission of his vasculitis he was switched to azathioprine for maintenance of remission. His renal function was stable with a serum creatinine of 1.3 mg/dl at the time of his last follow-up in October 2012.

Discussion

An annual influenza vaccination is recommended for all persons aged 6 months or older [5]. The vaccine consists of inactivated polyvalent preparations of antigens representative of influenza viruses that are expected to be prevalent. All seasonal influenza vaccines licensed in the United States are produced in hen's eggs and do not contain any adjuvants. Some multidose vaccines contain thiomersal, which is used as a preservative to prevent bacterial overgrowth. The vaccine is well tolerated with few side effects. The common side effects include local reactions with erythema and induration at the injection site. Systemic reactions are rare and include acute febrile illness, hypersensitivity reactions and Guillain-Barre syndrome (GBS). An even more rare association has been the assumed promotion of autoimmune phenomena ranging from clinically silent autoantibody production to full-blown autoimmune illness. Primary vasculitides including leukocytoclastic vasculitis, Henoch-Schönlein purpura, giant cell arteritis and microscopic polyangiitis have been described in temporal association with influenza vaccine administration. Clinical studies, *in vitro* experiments and animal models have confirmed a pathogenic role for ANCA in AAV. The initial descriptive cases of systemic small vessel vasculitis associated with immunization with influenza lack data on ANCA serology. The first case of AAV with positive ANCA serology after exposure to influenza vaccine was described in 2005 [6], but since then few additional cases have been published. We report 2 cases of AAV following influenza vaccination and provide a literature review including the 6 previously reported cases and speculate on mechanisms of influenza vaccine-associated vasculitis.

Influenza vaccination is considered to be safe and effective both for the general population and for patients with autoimmune rheumatic disease [7, 8]. Despite safety evidence of influenza vaccine usage in autoimmune disease, postvaccination autoimmune diseases have been reported. GBS has been the most frequently reported autoimmune disease to the Vaccine Adverse Events Reporting System since its inception in 1990. A statistically significant higher risk of GBS was reported with the use of swine influenza vaccine within 6–8 weeks after immunization. A study of seasonal influenza vaccines in the 1992–1993 and 1993–1994 seasons found a combined relative risk for GBS of 1.7 within 6 weeks of vaccination [9]. Influenza vaccination may be considered to be a two-edged sword in AAV patients. Infections remain a significant problem, contributing to increased hospitalizations and mortality

in AAV patients. An increase in disease activity has been described in autoimmune disease after influenza vaccination [10, 11]. The risk of multiple sclerosis relapse after influenza illness was greater than the potential for relapse after influenza vaccination and may be prudent with patients with moderate disability to reduce the increased risk of complications related to influenza illness [11]. A retrospective study looking at vasculitis relapse rates in AAV patients did not show an increase in relapse in AAV patients who were administered influenza vaccine compared to those who were not vaccinated [12]. Furthermore, a prospective study of influenza vaccination in patients with GPA with quiescent disease showed an adequate antibody response to the vaccine and no rise in disease activity following influenza immunization [13]. Therefore, the routine use of influenza vaccination in patients with autoimmune disease should be performed after careful assessment of the benefit-to-risk ratio.

The association between vaccines and induction of AAV may be mediated through several mechanisms. Vaccines often contain adjuvants which are used to prolong the immune response to the infectious antigen and thereby enable a decrement in the amount of required antigen. These adjuvants can provoke an autoimmune response and lead to autoimmune syndrome induced by adjuvants [14]. The influenza antigen and vaccine proteins share substantial structural similarity, which raises the possibility that the influenza vaccine can activate the same autoimmune mechanisms that are activated by infectious antigens. Both antigen-specific and antigen-nonspecific mechanisms are postulated to play a role in infection-induced autoimmunity [15]. Molecular mimicry is an antigen-specific phenomenon where there is activation of autoreactive B and T cells due to antigen similarity between the host antigen and microbial antigen. In addition, infection-related signals can also trigger innate immunity. Innate immunity enhances the immunogenicity of host antigens and may play a role in overcoming the regulatory pathways that limit the autoimmune response. There could also be antigen-nonspecific mechanisms in which the vaccine provides a transient inflammatory setting for bystander activation resulting in release of previously sequestered self-antigens or stimulating an innate immune response [15, 16].

The induction of AAV involves a complex interplay of environmental factors in a genetically predisposed individual with loss of immune tolerance. Although ANCA have been shown to be pathogenic, the cause of ANCA production remains unresolved. Naturally occurring ANCA have been demonstrated in healthy subjects [17],

Table 1. Characteristics of AAV following influenza vaccination

Age, years	Gender	Time from immunization to disease onset	New diagnosis/relapse	Disease type	ANCA type	Organs involved	Treatment	Outcome	Study
83	female	2 weeks	new	MPA	MPO	kidney, lung	CYC/P	remission	[5]
28	female	2 weeks	new	GPA	c/PR3	kidney, lung	CYC/P	remission	[19]
55	female	3 weeks	new	MPA	p/MPO	kidney, lung	CYC/P/PE	remission, dialysis independent	[19]
70	male	3 weeks	new	GPA	p/MPO	kidney	CYC/P	ESRD, death	[19]
67	female	12 days	relapse	GPA	c/PR3	kidney, lung	CYC/P	remission	[19]
20	male	NK	relapse	GPA	c	kidney, brain, GI tract, sinus	MMP/P/PE	death	[20]
50	male	2 weeks	new	GPA	c/PR3	kidney, joints	CYC/P	remission	current case
75	female	4 weeks	new	GPA	p/MPO	kidney, sinus	CYC/P/PE	ESRD, remission	current case

c = Cytoplasmic; CYC = cyclophosphamide; ESRD = end-stage renal disease; MMP = mycophenolate mofetil; MPA = microscopic polyangiitis; MPO = myeloperoxidase; NK = not known; p = perinuclear; P = prednisone; PE = plasma exchange; PR3 = proteinase 3.

leading us to believe that autoimmune disease is more likely due to dysregulation of natural homeostatic autoimmunity than onset of previously absent self-recognition. Furthermore, studies have demonstrated differences in the repertoire of epitope specificity of naturally occurring and pathogenic ANCA [18]. The transition from naturally occurring to pathogenic ANCA requires changes in immune regulatory mechanisms involving T and B cells. Ineffective T and B cell regulatory function has been demonstrated in AAV in a recent study by Free et al. [19]. This study showed an increase in circulating Tregs in active disease. However, these Tregs have a defective suppressor function. In addition, an expanded population of CD4+ cells resistant to Treg suppression and a decrease in regulatory B cells were demonstrated in active AAV. This ineffective T and B cell regulation may cause transition from natural to pathogenic ANCA [19]. Recent studies have shown an increase in Tregs and B regulatory cells in HIV-infected patients administered the H1N1 influenza vaccine [20]. We speculate that the abnormalities in Tregs and B regulatory cells leading to production of pathogenic ANCA may play a role in induction of AAV with influenza immunization. Another intriguing possibility for pathogenic ANCA production was proposed by Pendergraft et al. [21], who implicated peptides complimentary to autoantigens which serve as the initial impetus for production of pathogenic antibody

against the autoantigens. These complimentary peptides are products of transcripts of antisense DNA and can occur naturally, but can also be brought on by an infectious agent acting as an exogenous mimic of the complimentary peptide.

There are 8 reported cases of AAV after influenza vaccination, including our patients (table 1) [6, 22, 23]. In these patients, AAV occurred 2–4 weeks after vaccine administration. Both new cases and relapsing cases of AAV have been described. The median age at the time of presentation in these patients was 61 years with a female preponderance. The disease phenotype was GPA in 6 of 8 patients. In these cases, the ANCA type was equally distributed with 4 patients positive for cytoplasmic ANCA and 4 patients positive for perinuclear ANCA. The organs commonly affected by AAV include the kidneys and lungs. Treatment with cyclophosphamide and corticosteroids was effective for induction of remission of vasculitis in the majority of cases. Two patients reached end-stage renal disease. There were 2 deaths, one due to refractory vasculitis and the other due to bilateral pneumonia.

This report has obvious limitations. First, the small number of cases limits our ability to draw definitive conclusions and prove causality. These case reports can form the basis for formulating a hypothesis, but cannot be used to adequately test the hypothesis. In order to assess the relative risk of such vaccine-related adverse events, clinical

cal trials or epidemiologic studies with a large sample size are needed. Second, it is conceivable that more cases of influenza vaccine-associated AAV exist but go undiagnosed and unreported due to a lack of knowledge and rarity of this association. Fever, malaise, myalgia and other systemic symptoms, although rarely reported, may occur after influenza vaccination and not be ascribed to AAV.

In conclusion, the temporal association of AAV to influenza vaccination suggests that the vaccine might serve as a trigger for development of AAV in predisposed individuals. Vaccine genomic studies may help in identification of susceptible individuals. Epidemiologic studies looking at the prevalence of ANCA and AAV after influ-

enza vaccination and basic science studies to elucidate the mechanisms and immune responses to vaccine will help clarify if influenza vaccines predispose to AAV. In the absence of clear evidence of causality, from a population-based view, the preventative benefits and reduction in morbidity and mortality of influenza immunization in these high-risk individuals outweighs the occurrence of these rare but devastating autoimmune diseases.

Disclosure Statement

Duvuru Geetha served as a consultant and received honoraria for training the sales force for Genentech.

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