Case Report

Can influenza H1N1 vaccination lead to the membranous glomerulonephritis?

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ABSTRACT

In 2009 winter, Influenza A (H1N1) monovalent split virus vaccine was used prevalently in the whole world as a result of the pandemic caused by Influenza (H1N1) virus. The vaccine's adverse effects were observed closely and vaccination has been found as safe in most studies. But some reports about immune response related diseases after influenza vaccinations are remarkable. The close relationship between membranous glomerulonephritis and antigens is known, particularly in seconder forms which occur after viral infections and vaccinations. So this case report is about a 56-year-old man, who developed membranous glomerulonephritis 23 days after the vaccination against Influenza A (H1N1) virus.

KEY WORDS: Adverse effect, glomerulonephritis, H1N1 vaccination

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INTRODUCTION

Membranous glomerulonephritis (MGN) is one of the most common reasons for adult nephrotic syndrome (NS) and it is generally idiopathic. However, it may occasionally appear after viral infections such as influenza[1] and they are closely related with impaired immune response. The MGN which developed after the vaccination against influenza A (H1N1) virus that was brought to the agenda with pandemia in 2009 is presented in this report.

CASE REPORT

A 56-year-old male patient appealed to our clinic with the complaint of swelling on his feet and face. The patient developed influenza-like illness approximately 20 days after he was vaccinated with influenza vaccine that belonged to the year 2009. Following this, he had complained of pollakiuria, nocturia, and swelling on his feet and face. During this period, he had not received any kind of treatment before he came to our clinic.

There was no history of chronic illness, alcohol, drug or substance abuse except for 30 years' of smoking. His arterial blood pressure was 160/100 mmHg, pulse rate was 92 beats/min, and body temperature was 36.4°C. There were crackles at both of the lower lung fields and excessive pretibial edema bilaterally. There was no jugular venous distension. The other findings of physical examinations were normal. Serum creatinine and blood urea nitrogen levels were normal (0.9 mg/dl and 21 mg/dl, respectively), but the tests revealed hypoalbuminemia and proteinuria (serum albumin level was 2 gr/dl and urinary protein excretion was 7.3 gr/day) [Table 1]. Bilateral pleural effusion was present on chest X-ray. The kidneys looked normal in ultrasonography and minimal fluid was detected around his intestinal loops. There were not pathological findings in renal Doppler ultrasonography that was made as the patient had incipient and resistant hypertension.

Renal biopsy was performed in order to find out NS etiology. As a result of the research that was carried out through histopathologic and immunofluorescence staining methods, some findings in relation to MGN were detected [Figures 1 and 2]. The predominant finding by light microscopy was the thickening of the glomerular capillary wall. With the silver stain mild spikes were seen in the basal membrane. Immunofluorescence revealed granular global subepithelial deposits that stained strongest for Ig G and C3. Staining for C1q, Ig M, Ig A, or fibrinogen was negative. Staining with Congo-Red was negative in terms of amyloidosis. A medical treatment was arranged consisting of 10 mg/day lysinopryl, 40 mg/day atorvastatin, and 100 mg/day acetylsalicylic acid, and 1 mg/kg/day methyl prednisolone. Following this, edema and proteinuria of the patient subsided and his clinical condition improved. The patient's steroid dose was decreased gradually and stopped completely in the following three months. Within this period, renal functions of the patient were stable. Examinations conducted on the patient intended for the seconder causes of MGN were not significant (malignancies, rheumatologic

Table 1: Laboratory findings

Tests	*Normal ranges*	*Patient's values*
WBC (103/uL)	5.20-12.40	9.6
Hemoglobin(g/dL)	12-18	12.1
MCV (fL)	80-99	88
Thrombocyte (103/uL)	130-400	365
Glucose (mg/dL)	74-109	112
BUN (mg/dL)	6-20	12.1
Creatinine (mg/dL)	0.7-1.2	1.2
Total protein (g/dL)	6-7.8	4.1
Albumin (g/dl)	3.4-4.8	2
Total cholesterol (mg/dl)	120-200	425
LDL (mg/dL)	100-129	326
Urine density	1.010-1.020	1.020
Urine pH	4.8-7.4	5
Urine protein (g/day)		7.3

WBC = White blood cell; MCV = Mean corpuscular volume; BUN = Blood urea nitrogen; LDL = Low-density lipoprotein

disorders, or infections). In light of anamnesis and laboratory results, we deduced that MGN was related to the influenza vaccine shot 23 days before the symptoms appeared.

DISCUSSION

MGN, or membranous nephropathy as it is sometimes called, accounts for approximately 30% of cases of NS in adults, with a peak incidence between the ages of 30-50 years. Membranous nephritis is typically associated with immune deposits along the glomerular basement membrane. The main pathology in MGN is diffuse granular accumulation of IgG and C3 deposits and uniform thickening of the basement membrane that can be demonstrated by biopsy. In 25-30% of cases, MGN is secondary to malignancy (solid tumors of the breast, lung, and colon), rheumatologic disorders like lupus or rarely rheumatoid arthritis, or infection.[1]

The close relationship between this disease and antigens comes into prominence in their secondary forms, especially the ones that develop after viral infections. There are some cases of NS, acute glomerulonephritis, post-infectious glomerulonephritis that developed after viral infections such as Influenza A in the literature.[1] Besides, it has been accepted that after vaccinations, the risk of encountering immune response related diseases increases. For instance, Influenza vaccine is a risk for Guillain-Barré syndrome (GBS), which is an immunity related disease.[2] In recent years, NS cases have been reported to have developed after HBV, pneumococcus, and Influenza vaccinations.[3,4] While the reason for some of these cases was minimal change disease, the pathology of the others could not be defined. In 2000, Kielstein *et al*,[5] reported NS connected with minimal change disease after Influenza vaccination, and in 2002, Yanai-Berar *et al*,[6] presented leukocytoclastic vasculitis accompanied with pauci-immune crescentic glomerulonephritis. In 2004, Kao *et al*,[7] presented GBS accompanied with NS, and in 2005, Hyla-Klekot *et al*,[8] presented necrotizing glomerulonephritis cases which developed after Influenza vaccination. But a MGN case after Influenza vaccination as we presented was not reported in the literature before.

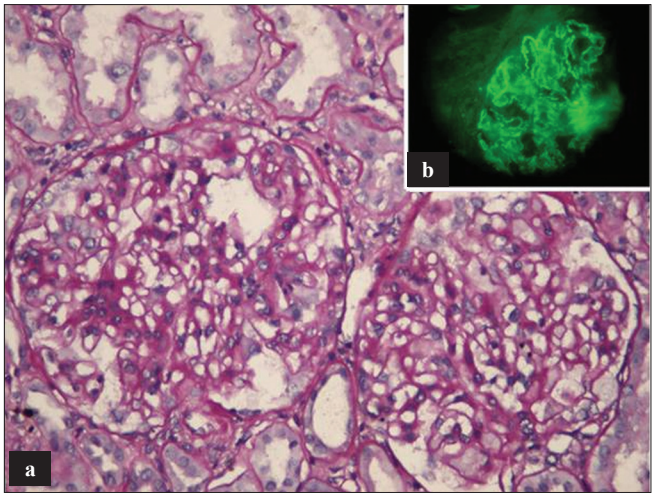

Figure 1: Microphotograph show that thickining the basal membrane of glomerules (a, PAS ×200) and granular Ig G deposites (b, IF) identified along with basal membrane. Mild mesangial hypercellularity was seen in a few glomerules and there were not seen amiloid deposition in kidney biopsy

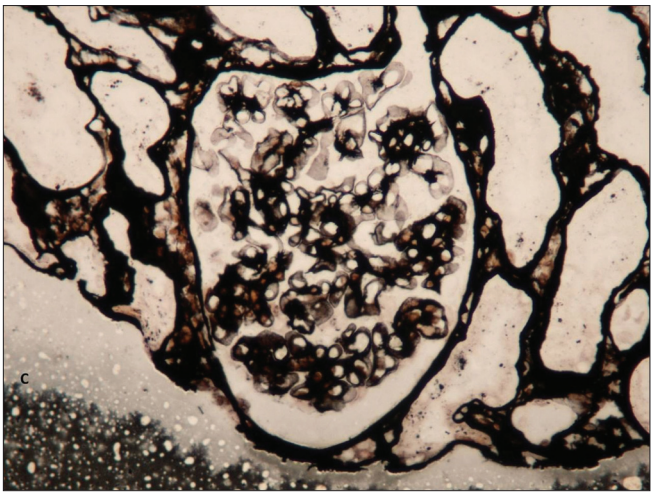

Figure 2: PAS and silver stains show that mild spikes and marked thick capillary wall in glomerule(C, PAS-M ×400)

In 2009 winter, Influenza A (H1N1) monovalent split virus was used prevalently in the whole world as a result of the pandemic caused by Influenza (H1N1) virus. A lot of researches have been carried out on the safety and immunogenicity of this vaccine and in many of them the vaccine has been found to be safe. One dose of vaccine was highly immunogenic in adults, suggesting that it afforded sufficient protection against this pandemic influenza A H1N1 virus. These studies also revealed that the immunogenic response to the vaccine develops on 23th day after vaccination.[9] In surveillance studies, some serious side effects such as GBS and anaphylaxis that are no different from seasonal Influenza vaccine were reported. However, nephropathy or related case was not reported.[9,10]

The MGN diagnosis that appeared with NS clinic and was confirmed through renal biopsy has been thought to be associated with 15 mg dose swine Influenza vaccine (*each 0.5 ml dose of 7.5 micrograms (H1N1) virus-like (X-181) strains and adjuvant MF59C*) inoculated to the patient 23 days before, since emergence of the illness and development of immunogenic effect of the vaccine occurred simultaneously. Watanabe *et al*,[11] reported that four patients exhibited purpura, three complained of arthralgias, and one had both abdominal pain and renal involvement after H1N1 vaccination. Reviewing the literature, 11 patients with HSP following influenza vaccination have been reported. Five of those 11 patients had past history of immunologically mediated disease including HSP, drug eruptions, and food allergy. While a favorable outcome was noted in most patients, one patient developed end-stage renal failure and another exhibited chronic glomerulonephritis.[11] Precise reason for MGN and renal involvement following H1N1 vaccination was unclear, but possible disposition to autoimmune renal disease appears to be the cause of MGN.

CONCLUSION

Although vaccines are some kind of divine efforts to prevent infections that may reach to pandemic level, they are also significant because of their side effects on mostly healthy people. The Influenza virus against which the human beings have been struggling for years came into prominence in 2009 because of the pandemic it caused. Fortunately, the disaster was avoided thanks to the vaccine. However, as in the presented case, the number of the cases of immune response related illnesses and renal diseases such as NS developing after the vaccine is gradually increasing. The growing role of the vaccines in NS and glomerulonephritis etiology is also striking.

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