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CASE REPORT

Onset of adult-onset Still's disease following influenza vaccination

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Abstract We describe that case of a 61-year-old woman who developed high spiking fever, sore throat, polyarthralgia, and salmon pink evanescent rash following influenza vaccination. A diagnosis of adult-onset Still's disease (AOSD) was made based on clinical and laboratory findings. Methylprednisolone pulse therapy followed by oral prednisolone resulted in a favorable outcome. This is the second published case in which a causal relationship between vaccination and onset of AOSD is suggested. Bystander activation would appear to play an important role in inducing the immune reaction.

Keywords Adult onset Still's disease · Influenza vaccine · Cytokines · Bystander activation

Introduction

Adult-onset Still's disease (AOSD) is an inflammatory disease of unknown etiology characterized by high spiking fever, polyarthralgia, and salmon pink evanescent rash. Levels of inflammatory cytokines, such as interleukin (IL)-1, IL-6, interferon-γ, and tumor necrosis factor-α, are elevated in patients with AOSD [1] and appear to play an important role in the pathogenesis of this disease. Although viral infections, such as parvovirus B19 [2], rubella [3], coxsackie virus [4], adenovirus [5], and mumps [6], have been postulated as an etiology, a definitive causative agent has not yet been identified.

Influenza vaccine is widely used to prevent/mitigate the serious complications related to influenza. Although influenza vaccination is considered safe, case reports of autoimmune adverse events, such as Guillain–Barré syndrome (GBS) [7], acute disseminated encephalomyelitis (ADEM) [8], systemic lupus erythematosus [9], microscopic polyangiitis [10, 11], and idiopathic thrombocytopenic purpura (ITP) [12, 13], have been reported. In 2010, Yoo [14] reported the first case of AOSD following influenza vaccination.

Here, we report the second case of AOSD following influenza vaccination and discuss the causal relationship between the onset of AOSD and influenza vaccination. We also discuss the mechanisms by which influenza vaccination induced the immune reaction in our patient.

Case report

A 61-year-old woman was admitted to our hospital with high spiking fever, sore throat, polyarthralgia, and salmon pink evanescent rash. She had undergone surgery for colon cancer 5 years previously. The postoperative course was uneventful, with no recurrence of the disease. She had never suffered from influenza infection.

She received influenza vaccination [KAKETSUKEN, Kumamoto, Japan; A/California/7/2009(H1N1), A/Victoria/210/2009(H3N2), and B/Brisbane/60/2008] at the beginning of the November 2010. The vaccine contains minute amounts of formaldehyde, phenoxyethanol, sodium chloride, sodium hydrogen phosphate, and potassium dihydrogenphosphate as additives. Our patient was

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standardly vaccinated for seasonal influenza every year and had received the pandemic influenza A (H1N1) vaccine in 2009, without any noticeable adverse effect. She developed high fever 1 day after receiving the vaccination and a severe sore throat, polyarthralgia in the shoulders, elbows, wrists, hands, and knee joints, and evanescent rash on the forearms the day thereafter (2 days after vaccination). She visited her family physician; tests for influenza antigen was negative and she was diagnosed with a cold. She was treated with antibiotics and non-steroidal anti-inflammatory medications, without noticeable effects. Nine days after receiving the influenza vaccine, she presented to our hospital and was admitted for further evaluation and treatment.

At the time of admission, she looked distressed and her blood pressure was 104/70 mmHg with a pulse rate of 80 per minute. Her body temperature increased to as high as 38.8° in the evening, at which time multiple papular erythema with fusion tendency were noted on the forearms (Fig. 1); these disappeared when she became afebrile the following morning. The remainder of the physical examination was unremarkable.

The results of the laboratory tests were as follows: mild leucocytosis (11,090/μl); mildly decreased platelet count (132,000/μl); mildly elevated levels of transaminases; moderately elevated levels of lactate dehydrogenase (LDH, 566 IU/l) and C-reactive protein (CRP, 8.01 mg/dl). The serum ferritin level was markedly elevated (15210 ng/ml), while serum levels of serum C3 and C4 were mildly elevated. Renal function was normal. Tests for anti-nuclear antibody, proteinase 3-antineutrophil cytoplasmic antibody (ANCA), and myeloperoxidase-ANCA were all negative. Results of serological tests for Epstein–Barr (EB) virus-related antibodies were as follows: titers of immunoglobulin G (IgG) antibody to viral capsid antigen (VCA), 160; IgM to VCA, >10; EB nuclear antigen (EBNA), 20. Tests for IgM antibodies against viral infection, such as parvovirus, rubella, herpes simplex virus, and cytomegalovirus, were all negative, as were the cultures for bacteria in the blood and urine. There were no abnormal findings on the computed tomography scan except for moderate splenomegaly. Drug allergy was ruled out because characteristic symptoms of AOSD occurred before any medications were administered. Thus, a diagnosis of AOSD was confirmed.

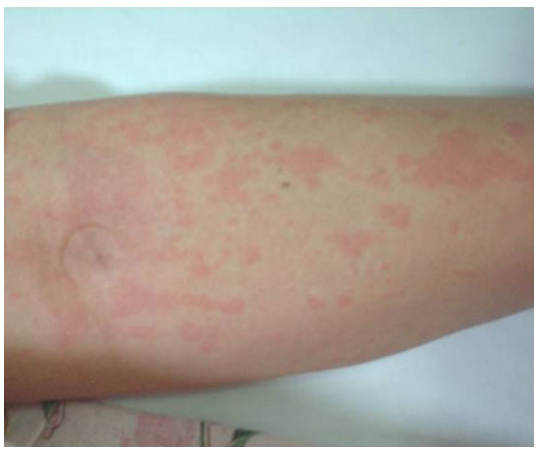

Fig. 1 Multiple papular erythema with fusion tendency on the forearms of our patient during a period of spiking fever

She was treated with a 3-day course of methylprednisolone pulse therapy (1 g daily) followed by prednisolone at 40 mg daily. The fever subsided soon after the first administration of methylprednisolone. The rush, sore throat, and arthralgia subsequently disappeared together with the normalization of LDH, CRP, and ferritin levels.

Discussion

The potential association between vaccination and onset of immune-mediated disease has been suggested based on a temporal relationship, however, the lack of experimental and epidemiological evidence makes it difficult to establish a causal relationship. In the present case, the patient developed characteristic symptoms of AOSD 1 day after receiving influenza vaccine. The strong temporal relationship prompted us to suspect a causal relationship between the onset of AOSD and influenza vaccination. Yoo [14] reported a similar case in which a 73-year-old woman developed AOSD 2 days after influenza vaccination. Although the development of AOSD in these two patients within a very short time following influenza vaccination may just be coincidental, the possibility seems very low because AOSD is a rare disease. Thus, we have to consider the possibility that influenza vaccination is causally related to the onset of AOSD.

Viral infection is thought to induce or trigger an autoimmune reaction by molecular mimicry or bystander activation [15]. Molecular mimicry can trigger autoimmunity when partial homology exists between the viral antigen and self antigen; the immune response directed against the viral antigen can then also be directed against the self antigen, initiating autoimmune disease. Thus, molecular mimicry can break down tolerance to self antigens. This mechanism differs from that by which bystander activation can trigger an immune reaction. Viral infection can induce a native immune reaction with enhanced cytokine production by macrophages and destroy both normal and infected cells, possibly resulting in the release of sequestrated antigen. This process activates preexisting autoreactive T cells, which further enhance cytokine production, resulting in progression of the immune reaction.

It has been reported that vaccinations, such as those for viral infections, can activate the immune response and induce immune-mediated disease by molecular mimicry or bystander activation [16]. Because targeted self antigen is identified in some of the influenza vaccine-associated diseases, such as ganglioside in GBS, myelin in ADEM, and plycoprotein in ITP, such diseases are likely to be induced predominantly by molecular mimicry. However, molecular mimicry alone is usually, if not always, insufficient to induce autoimmune disease [17]. Therefore, the bystander mechanism may be also involved. Immune-mediated diseases are induced by a number of vaccines other than that for influenza; these include multiple sclerosis after hepatitis B vaccination [18] and ITP after measles/mumps/rubella vaccination [19]. However, to the best of our knowledge, there has been no report describing the induction of vaccine-associated disease predominantly by bystander activation.

The etiology of AOSD is unknown, and it may not be an autoimmune disease because targeted self antigen has not yet been identified, which seems to provide evidence against the molecular mimicry mechanism. In addition, molecular mimicry usually requires several weeks to induce an autoimmune reaction, as exemplified by the onset of vaccine-associated GBS, the peak of which is the second week after the vaccination [7]. However, our patient developed AOSD 1 day after the vaccination, suggesting that a mechanism other than that of molecular mimicry is involved.

Viral infection has been postulated as an etiology of AOSD, with inflammatory cytokines playing an important role in its pathogenesis. Therefore, AOSD can be considered to be a macrophage activation syndrome (MAS), which is characterized by the activation of macrophages and excessive inflammatory cytokines [20]. Macrophage activation occurs as an ordinary protective immunity measure against viral infection. As such, it is possible that AOSD is not an autoimmune disease, but an extreme end of the protective immunity spectrum. Because vaccinations can elicit the same immune reaction as viral infection, it is conceivable that vaccinations trigger the macrophage activation. We speculate that, in our patient, influenza vaccination activated macrophages and probably preexisting autoreactive T cells and induced AOSD.

Viral-associated hemophagocytic syndrome (VAHS) is considered to be one a MAS, and clinical features of VAHS are similar to that of AOSD. Therefore, it is possible that our patient developed VAHS following vaccination. However, since the most characteristic feature of VAHS is leucopenia, VAHS is unlikely.

In summary, we have treated a patient who developed AOSD following influenza vaccination. A causal relationship between the vaccination and onset of AOSD is strongly suggested, and bystander activation seems to play an important role in inducing or triggering autoimmunity. Further experimental and epidemiological studies are necessary to confirm the causal relationship between influenza vaccination and onset of AOSD.

Conflict of interest None.

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