The inactivated influenza vaccine is considered to be well tolerated, with mild, local, and transient adverse reactions. Serious side effects are rare, and include severe allergic reactions and neurological manifestations such as Guillain-Barre syndrome and Bell’s palsy. Reports in the medical literature of autoimmune diseases associated with the influenza vaccine are scarce. We describe a patient who developed two episodes of adult Still’s disease (ASD) following influenza vaccine during the winters of 2018 and 2019.

PATIENT DESCRIPTION

In December of 2018, a 66-year-old female was admitted to our department due to fever of unknown origin (FUO). Her fever had started 5 weeks before her admission and was accompanied by general weakness and polyarthritis of the small joints of her palms and soles, which subsided after 3 weeks without any additional complaints.

On admission to our department, the patient was febrile (39.4°C) and tachycardic (125 beats per minute). The physical examination was normal. Laboratory tests showed a normocytic, hypoproliferative anemia (Hb = 7.6 g/dl), mildly elevated liver enzymes, lactate dehydrogenase 444 (IU/I), ferritin = 21,000 ng/dl, C-reactive protein (CRP) = 260 mg/L, and erythrocyte sedimentation rate (ESR) = 110 mm/hr. A workup for FUO included blood culture, serology for hepatitis viruses, Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus, syphilis, brucella, bartonella, leptospira, toxoplasmosis, West Nile virus, Mantoux test, protein electrophoresis, antinuclear antibody, anti-neutrophil cytoplasmic antibodies, antiphospholipid antibodies, complement levels, cardiac echography, and total body computed tomography (CT). All tests were without abnormal findings, except for mild lymphadenopathy in the right axilla and mediastinum that was seen on the CT scan. During that hospitalization the fever spontaneously and gradually subsided with parallel improvement in her symptoms and laboratory tests and the patient was discharged for ambulatory follow-up.

The following winter, December of 2019, the patient was hospitalized in our department again with a similar presentation of fever, arthritis, and weakness. This time the symptoms were accompanied with sore throat and weight loss. She reported receiving the influenza vaccine a week before her symptoms began, and when receiving this vaccination, she recalled that her initial episode, in December of 2018, also occurred shortly after receiving the influenza vaccine. Her physical examination revealed a salmon-colored rash over her upper chest [Figure 1A] and abdomen [Figure 1B]. Laboratory results demonstrated anemia (Hb = 8.2 g/dl), mildly elevated liver enzymes, CRP of 302 mg/L, and a very elevated ferritin level of 65,450 ng/dl. Repeated serology as described during her first hospitalization was negative. Total body CT showed diffuse nonspecific lymphadenopathy without hepatosplenomegaly. Subsequent bone marrow biopsy demonstrated a reactive morphology and excisional lymph node biopsy displayed reactive lymphadenopathy.

Based on these findings, the patient was diagnosed with ASD and treatment with high dose steroids (prednisone 80 mg/dl) was initiated, followed by a tapering regimen. After the initiation of prednisone, her symptoms resolved quickly, and her laboratory abnormalities gradually normalized. During the tapering regimen, she had two flares manifested by fever and arthralgia, which lasted for...
a few days. Both episodes were resolved following an increase in steroid dose. During her last clinic follow-up in May 2020, the patient reported feeling well, while receiving a prednisone dose of 10 mg/day. Her ferritin level was 300 ng/dl and inflammatory markers were within normal limits.

**COMMENT**

We report a patient who developed two bouts of ASD, shortly after the administration of the influenza vaccine, on two consecutive winters. An association between vaccines and autoimmune diseases is a well-described phenomenon. It is reasonable to assume that the influenza vaccine, which was administered a few days prior to the development of her symptoms on two separate occasions, triggered her autoimmune disease.

ASD is a rare inflammatory disorder with an unknown etiology. Both genetic factors and a variety of infectious triggers are suggested as possible etiologies. Proposed pathogens include viruses (rubella, echovirus, and measles) and bacteria. The main clinical characteristics of ASD include daily spiking fever, which usually precedes other manifestations, a cutaneous evanescent salmon-pink maculopapular eruption, most often present during febrile hours, arthritis (ranging from mild, transient and oligo-articular to severe, potentially destructive polyarthritis) and lymphadenopathy, that may lead to an erroneous diagnosis of lymphoma. Laboratory findings are characterized by marked elevation of CRP, ESR, and ferritin levels, normocytic, normochromic anemia, leukocytosis, and reactive thrombocytosis. The diagnosis of ASD is, in part, a diagnosis of exclusion, which can generally be made based upon the presence of the characteristic clinical and laboratory features, in the absence of other conditions that may cause similar symptoms and findings.

Several diagnostic criteria have been proposed, but none of them has sufficient sensitivity or specificity. The Yamaguchi criteria have the highest sensitivity in patients with a definite diagnosis of ASD. These include:

- Four major criteria
  - Fever of at least 39°C lasting at least 1 week
  - Arthralgia or arthritis lasting 2 weeks or longer
  - Nonpruritic macular or maculopapular skin rash that is salmon-colored in appearance and usually found over the trunk or extremities during febrile episodes
  - Leukocytosis (10,000/µl or greater) with at least 80 percent granulocytes
- Five minor criteria
  - Sore throat
  - Lymphadenopathy
  - Hepatomegaly or splenomegaly
  - Abnormal liver function studies, particularly elevations in aspartate and alanine aminotransferase and lactate dehydrogenase concentrations
  - Negative tests for antinuclear antibody and rheumatoid factor.

The diagnosis requires the presence of five features, with at least two being major diagnostic criteria, and exclusion of other rheumatic disorder known to mimic ASD. Our patient fulfilled most major and minor criteria.

ASD following influenza vaccination was reported previously in two other cases: a 72-year-old south-Korean female and a 61-year-old Japanese female. Association between inactivated influenza vaccine and various other autoimmune diseases has also been described, such as the case of a 55-year-old woman who developed SLE/APS-associated diffuse neurological symptoms after receiving the vaccine.

Several mechanisms for autoimmunity induced by vaccines were proposed:

- Partial homology between the viral antigens (or the adjuvant) and a self-antigen causing activation of the immune system against self-antigens (molecular mimicry)
- Over-production of cytokine-release that may destroy both normal and infected cells leading to the release of a sequestrated antigen that further enhance the autoimmune reaction
- Viral infection has been postulated as an etiology of ASD, with inflammatory cytokines playing an important role in its pathogenesis. In this regard, ASD may be considered a macrophage activation syndrome (MAS) characterized by the activation of macrophages and excessive inflammatory cytokines, leading to the activation of autoreactive T cells. As such, it is possible that ASD is not an autoimmune disease, but rather an extreme immune reaction aimed at protection from foreign material. Since vaccinations can elicit the same response as viral infections, it is possible that in our patient the influenza vaccine induced a limited MAS response manifested as ASD.

**CONCLUSIONS**

ASD is a very rare complication of influenza vaccination. Our case highlights two important issues: the potential of vaccines to trigger autoimmune diseases and the importance of taking a meticulous history of recent vaccinations in every patient with suspected autoimmune disease or FUO.

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