SHOENFELD´S SYNDROME AFTER PANDEMIC INFLUENZA A/H1N1 VACCINATION

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Abstract

Recently, reports have suggested grouping different autoimmune conditions that are triggered by external stimuli as a single syndrome called autoimmune/inflammatory syndrome induced by adjuvants (ASIA). This syndrome is characterized by the appearance of myalgia, myositis, muscle weakness, arthralgia, arthritis, chronic fatigue, sleep disturbances, cognitive impairment and memory loss, and the possible emergence of a demyelinating autoimmune disease caused by systemic exposure after vaccines and adjuvants. In the current study, the authors reported the first Brazilian case of a woman who developed ASIA, which was characterized by arthralgia, changes in inflammatory markers, and chronic fatigue, after the pandemic anti-influenza A/H1N1 vaccine without causing any other rheumatic disease, and it had a positive outcome.

Keywords: Pandemic H1N1 Influenza; Vaccination.

Introduction

A new influenza pandemic originated in North America during June of 2009, quickly spread throughout the world and resulted in a high mortality in young adults, especially in pregnant women and patients with chronic diseases[1]. It was nicknamed «Swine flu» and was soon identified as an epidemic of the influenza A/H1N1 virus without any regard to the cross-transmission by other animals. Laboratories quickly produced specific vaccines, and after preliminary studies on its immunogenicity and safety, the vaccines were released for mass immunization. The World Health Organization (WHO), which was already on high alert and modeling their control strategy on the H5N1 bird flu, called for the vaccination of the population, primarily the vaccination of professionals, those suffering from chronic diseases, pregnant women and other groups at risk, to contain the pandemic[1,2]. Currently, vaccination appears to be an efficient tool for controlling pandemic influenza A/H1N1, which still presents cases in India and Oceania[3]. WHO and its Global Advisory Committee on Vaccine Safety contend that monovalent anti-influenza vaccines, for influenza A/H1N1, produced from adjuvant or non- adjuvant viral fragments, are as safe and effective as the use of seasonal influenza polyvalent vaccines in the general population. Furthermore, its side effects are primarily local, minor and of short duration, such as pain at the injection site, a low-grade fever, coryza and myalgia and, very rarely, an allergic phenomena, such as urticaria, edema or bronchospasm. They also argued that adverse effects are less common than with other live virus vaccines. The adjuvants that are added by some manufacturers to reduce the amount of antigens used to stimulate and increase the immune response have been proven safe for use in immunization programs associated with other pathologies[4-6]. However, these same references warn that preclinical and clinical studies would not be able to identify all of the rare events that could occur during the application in a mass population, and they recommended a comprehensive surveillance system to collect information regarding the most serious post-vaccination effects, which in Brazil is coordinated by the National Agency of Sanitary Surveillance Agency (ANVISA)[7,8].

Recently, Shoenfeld suggested grouping different autoimmune conditions that are triggered by external stimuli as a single syndrome called autoimmune/inflammatory syndrome induced by adjuvants (ASIA). This syndrome is characterized by clinical manifestations, such as myalgia, myositis, muscle weakness, arthralgia or arthritis, chronic fatigue, sleep disturbances, cognitive impairment and memory loss, as well as pos-

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sible emergence of either a demyelinating or systemic autoimmune disease after exposure to vaccines and adjuvants (Table I)[9,10].

In this article, the authors describe the case of a woman who developed an atypical presentation of ASIA with arthralgia, changes in inflammatory markers, and chronic fatigue after administration of the pandemic anti-influenza A/H1N1 vaccine. The vaccine did not cause any other currently known rheumatic disease. This clinical case helps to establish the diagnosis of an auto-inflammatory syndrome induced by adjuvants, according to Shoenfeld's criteria[9].

Case report

We describe a case of a 44-year-old female patient, with a history of allergic rhinitis, hyperprolactinemia and systemic arterial hypertension, treated with 25-mg/day of atenolol for seven years, and history of a single episode of idiopathic uveitis on her left eye and treated without sequelae more than fifteen years ago. Two years before this, she had a history of trivalent seasonal influenza vaccinations without any reports of adverse reactions. Her mother has rheumatoid arthritis. The patient had been immunized with a single 3.75 µg dose intramuscularly with the monovalent vaccine strain, H1N1/California/7/2009 virus, which was propagated in eggs containing the AS03 squalene as an adjuvant, two weeks prior to the development of acute symptoms and the rapid progression of the complains. The patient presented with chronic fatigue not relieved after rest, myalgia, muscle weakness, diffuse arthralgia in her hands, wrists, ankles and feet, with inflammatory characteristics and neck pain. Upon examination, the pain was expressed in all proximal interphalangeal, second, and third metacarpophalangeal joints symmetrically. The patient also had painful palpation of the metatarsal and calcaneal region, without pain with ankle mobilization. We also found tender points located at the upper edge of the trapezoid, all bilaterally and on the epicondyle side. C-reactive protein (CRP) levels increased early, followed by a significant increase in the erythrocyte sedimentation rate (ESR). On the 21st, 30th, 60th, and 90th days after immunization the CRP levels were 1.03 mg/L, 2.36 mg/L (maximum), 1.66 mg/L and 0.15 mg/L (normal value <0.5 mg/L); and, moreover, the ESR of 25 mm/1st hour, 37 mm/1st hour, 41 mm/1st hour (maximum), and 9 mm/1st hour rates, respectively (Figure 1). The patient had a negative rheumatoid factor and negative anti-CCP antibodies with the absence of hypergammaglobulinemia, antinuclear antibodies, and anti-Ro/SS-A antibodies. Serologies for toxoplasmosis, Epstein-Barr virus, cytomegalovirus, parvovirus B19, HIV, and Hepa-

Table I. Criteria suggested by Shoenfeld for ASIA diagnosis

Major criteria:

- Exposure to an external stimuli (infection, vaccine, silicone, or adjuvant) prior to clinical manifestations
- Appearance of one of the clinical manifestations listed below:
  - Myalgia, myositis, or muscular weakness
  - Arthralgia and/or arthritis
  - Chronic fatigue, non-restful sleep, or sleep disturbances
  - Neurological manifestations (especially those associated with demyelization)
  - Cognitive alterations and loss of memory
  - Fever and dry mouth
- Removal of the initiating agent induces improvement
- Typical biopsy of the involved organs

Minor criteria:

- Appearance of autoantibodies directed against the suspected adjuvant
- Other clinical manifestations (e.g., irritable bowel syndrome)
- Specific HLA (e.g., HLA DRB1, HLA DQB1)
- Initiation of an autoimmune illness (e.g., multiple sclerosis or systemic sclerosis)

For the diagnosis of ASIA, the presence of at least 2 major or 1 major and 2 minor criteria must be apparent. This is a reproduction obtained with the author's permission.

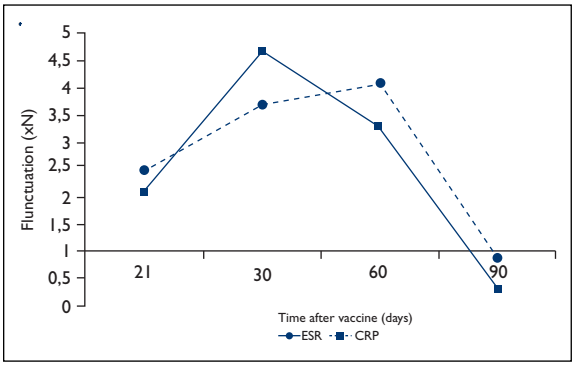

Figure 1. The evolution of inflammatory biomarkers after vaccination

N: reference value adjusted for 1 unit; xN: times the normal upper limit value; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

titis B and C were also negative. Normal thyroid hormones and a slight increase of prolactin (29.47 ng/mL compared to a normal value of <20 ng/mL) were observed. The initial radiological evaluation of the hands, wrists, ankles, and feet showed no abnormalities. The diagnosis of Shoenfeld's syndrome or an autoimmune/inflammatory syndrome induced by adjuvants was performed based on Shoenfeld's proposed criteria[9] (Table I). The patient was treated with 1 g paracetamol three times daily, 400 mg ibuprofen four times daily for the first few months, and 400 mg hydroxychloroquine daily, and a gradual improvement of pain was observed after four weeks of anti-malarial drug administration. Chloroquine was used trying to block the autoimmune mechanisms and seemed to be successful. No significant new complaints appeared during the two months after starting the treatment. The evolution of the pathology had a significant impact on the daily functional and work activities of the patient. Currently, the patient was able to complete her important daily activities with no need to control the pain and did not present any new symptoms.

Discussion

The authors describe the first case of post-vaccination ASIA in Brazil for prophylaxis pandemic influenza A/H1N1 recommended for application in mass population situation officially declared pandemic.

This patient developed symptoms abruptly (fourteen days after vaccination of the monovalent adjuvanted anti-influenza A/H1N1 by compound squalene). These symptoms were chronic fatigue syndrome with arthralgia, myalgia, chronic fatigue no relieved after rest and difficulty maintaining their usual activities. The patient had never presented similar symptoms, had no standardized number of tender points that were sufficient for a diagnosis of fibromyalgia, and had no important local reaction and high inflammatory activity at the vaccination site. In addition, the patient had no criteria suggesting a manifestation of early rheumatoid arthritis, scleroderma, polymyositis, systemic lupus erythematosus or any other systemic collagen-specific pathology. These findings led the authors to consider ASIA[9] (Table I).

A clear temporal relationship herein observed exists between the immunogenic vaccine and the degree of the functional impairment and it was seen two weeks after vaccination. The association between the vaccination and the onset of autoimmune manifestations have been described in the literature like the reaction to the vaccination against seasonal influenza and cases of Guillain-Barre[10], inflammatory myopathy triggered by the adjuvant aluminum in vaccines administered in France[11], and compulsory immunization in polyform sent to military operations in the Persian Gulf[12], namely the vaccination against anthrax. Specific antibodies against major adjuvants have been isolated from healthy vaccine recipients, and extensive discussion has been conducted on the meaning of these clinical findings[12,13]. However, these occurrences are more frequent when associated with rare genetic preconditions in the general population, which was observed with myositis in the macrophage caused by aluminum[11].

The relationship between infections with viral agents that serve as a trigger for self-harm responses and the subsequent development of autoimmune changes can be caused either directly by infection with an impairment of lymphocyte function or cytolysis with intracellular exposure. For several other mechanisms to stimulate the aberrant production of autoantibodies and chemotropic, a phenomenon must occur that is independent of viral replication and, therefore, may occur after exposure of the fractions found in inactivated viral vaccines[14]. The increase in the immune response is the purpose of the use of adjuvants. Although they are considered safe for use on a large scale, they are not absolutely free of side ef-

fects[13,15,16]. The assessment of the safety of the influenza vaccine and adjuvants were not exhaustive due to the fast response, production, and marketing that was required by the pandemic[2]. Furthermore, their use was excluded from trials of individuals with a history of atopy or prior immunodeficiency (congenital or acquired) or patients that were receiving immunosuppressive therapy or steroids prior to vaccination[17].

Although does not exist clear evidence that the vaccination against influenza A/H1N1 could trigger the onset or aggravate the course of an autoimmune disorder in recipients receiving the vaccine, fear remains that preventive viral immunization is the biological stimulus that is sufficient to trigger an atypical autoimmune reaction with a disproportionate risk/benefit ratio for the target.

To our knowledge, after the pan-immunization campaign against the recent influenza H1N1 virus in this country, no published cases of a similar reaction have been reported. The diagnosis applied to this case is recognized as the first Shoenfeld's syndrome case reported in Brazil.

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