IMAJ • VOL 18 • MARCH-APRIL 2016

Autoimmune/Inflammatory Syndrome Induced by Adjuvants and Sjögren's Syndrome

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ABSTRACT: Sjögren's syndrome (SS), a chronic systemic autoimmune inflammatory condition involving the exocrine glands, has been suggested to be part of the spectrum of the Autoimmune/inflammatory Syndrome Induced by Adjuvants (ASIA). ASIA incorporates an umbrella of clinical conditions including siliconosis, macrophage myofasciitis syndrome, and post-vaccination phenomena that occur after the exposure to a substance, namely the adjuvant. Interestingly, SS and ASIA share several common features. Firstly, a shared pathogenic mechanism involving a disruption of the immune system balance, with B cell proliferation, cytokine production and tissue infiltration, has been proposed. Patients with ASIA often present clinical features resembling those of SS; dry mouth and dry eyes have also been included in the proposed classification criteria for ASIA. Finally, several case reports have suggested that both vaccines and silicone may trigger the development of SS. Unveiling these common pathways will contribute considerably to our understanding and management of both conditions.

IMAJ 2016; 18: 150–153

KEY WORDS: autoimmune/inflammatory syndrome induced by adjuvants (ASIA), Sjogren's syndrome (SS), vaccine, autoimmunity, adjuvants

In 2011 a new term, "Autoimmune/inflammatory Syndrome Induced by Adjuvants" (ASIA) was coined to illustrate a spectrum of clinical conditions sharing similar signs or symptoms [1]. These disorders – including siliconosis, Gulf War Syndrome (GWS), macrophage myofasciitis syndrome (MMF), sick building syndrome (SBS), and post-vaccination phenomena – all develop following the exposure to a common denominator: the adjuvant. The adjuvant, defined as "any substance that acts to accelerate, prolong, or enhance antigen-specific immune response" [2], has the property to boost the immune response without having any specific antigenic effect itself. Because of this property, the adjuvant is considered a key factor able to stimulate the onset of such diseases. The clinical conditions included in the ASIA spectrum represent immune mediated disorders that usually appear following a chronic stimulation of the immune system by agents with adjuvant characteristics. A wide range of symptoms have been described, including myalgia, myositis, arthralgia, neurologic manifestations, fever, dry mouth, cognitive alterations, as well as chronic fatigue syndrome. In order to diagnose ASIA, major and minor criteria have been suggested, including the above mentioned symptoms as well as the presence of autoantibodies or antibodies directed at the suspected adjuvant or specific HLA (i.e., HLA DRB1, HLA DQB1) [1]. For these conditions to develop, the existence of a predisposing genetic background as well as different external or endogenous environmental agents are necessary. The trigger role of external factors is essential in this setting; several of them have been recognized and are included in a group of agents termed the "exposome" [3]. The evidence of a predisposing genetic background not only provides an explanation for the rarity of ASIA syndrome but also clarifies why physicians should be aware of the existence of this possible complication following vaccine exposure in specific individuals [4].

The most common agents acting as adjuvants are silicone, aluminum, pristane, and infection. One of the principal mechanisms of action is represented by molecular mimicry. Basically, molecular mimicry refers to the way in which the immune response, initially directed against bacterial or viral antigens, can target host molecules sharing sequence homology or structural similarities with microbial epitopes [2]. Other mechanisms of actions have also been described, including B cell polyclonal activation, bystander activation (which enhances cytokine production and induces the expansion of autoreactive T cells), and epitope spreading whereby invading antigens accelerate the local activation of antigen-presenting cells and the over-processing of antigens [4].

Aluminum is one of the principal adjuvants used in vaccine formulation and may be responsible for the development of ASIA syndrome. It seems that its ability to behave as an adjuvant might be related to evidence that aluminum salts seem to both induce the activation of dendritic cells and complement components and increase the level of chemokine secretion at the injection site [5].

Also, exposure to silicone is believed to boost the immune response. Silicone is considered an inert material, and for this reason has been incorporated in different medical products and devices such as breast implants. Following a prosthesis