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

break, local cutaneous inflammation, regional lymphadenopathy and silicone granuloma have been reported; also described is the remission of these conditions after implant removal. It seems that silicone implants trigger a specific antigen-driven local immune response through activated Th1/Th17 cells [6]. Moreover, patients with severe immune mediated reactions to implanted silicone devices were found to have increased immunoglobulin G in the surrounding tissue and higher levels of anti-silicone antibodies [7]. These findings suggest a possible adjuvant action of silicone.

Interestingly, most of the clinical features included in the ASIA criteria, such as dry mouth and/or dry eyes, myalgia and/or muscle weakness, arthralgia and/or arthritis and fatigue, are typical manifestations of patients with Sjögren's syndrome (SS). For this reason, it would be interesting to analyze the possible connection between these two disorders, which might be related to each other from both a pathogenic and clinical point of view.

PATHOGENESIS OF SJÖGREN'S SYNDROME AND ADJUVANTS

SS is a chronic autoimmune inflammatory disease characterized by the presence of lymphocyte infiltrates in the salivary glands. Once started, the ongoing inflammatory reaction leads to a progressive glandular dysfunction with consequent onset of sicca symptoms. In some patients extra-glandular manifestations occur, leading to life-threatening complications in rare cases. A key role is played by the activated epithelium, and several studies over the years have underlined the very high expression of the type I interferon (IFN) pathway in both peripheral blood mononuclear cells and minor salivary gland biopsies, supporting a role for the IFN 'signature' in the pathogenesis of the disease. As mentioned above, the activated epithelium is indispensable for disease onset, and the expression by these cells of Toll-like receptors (TLRs) and MHC class I and II molecules is essential for the presentation of autoantigen and production of pro-inflammatory cytokines. Among these molecules, the production of B cell-activating factor (BAFF) by epithelial cells greatly contributes to the stimulation of the adaptive immune system and the potential development of lymphoma. Indeed, B lymphocytes have a central role in the development of the disease [8].

It has been suggested that both genetic [9] and environmental factors are responsible for SS development. Among the environmental agents, infections seem to be the most important trigger of disease. Indeed, several infections may mimic SS, including tuberculosis, leprosy, spirochetes, hepatitis A, B or C, parvovirus B19, Dengue fever, malaria, subacute bacterial endocarditis, and human immunodeficiency virus (HIV) [10]. In such conditions, viruses expressing a specific tropism for salivary and lachrymal glandular tissue play a key role in activating the immune response. The main responsible viruses are cytomegalovirus (CMV), Epstein-Barr virus (EBV), and human herpes virus (HHV) 6, 7 and 8. These viruses are able to induce activation of the innate immune system via TLR pathways, which consequently stimulate the production of chemokines and cytokines whose expression is up-regulated in labial salivary glands, plasma and peripheral blood cells of SS patients. Therefore, it should not be surprising for SS to develop, albeit rarely, following the administration of a vaccine [11].

SJÖGREN'S SYNDROME AND VACCINES

Some studies in the literature have reported the possible onset of SS following vaccine exposure [Table 1]. According to the recommendation on vaccine administration in patients with rheumatic diseases [12], several vaccines should be strongly considered in SS (such as the influenzae, the 23-valent polysaccharide pneumococcal, herpes zoster, and tetanus toxoid vaccinations). However, other vaccines including Bacillus Calmette Guérin (BCG), hepatitis A and/or B and human papillomavirus, should be avoided or considered only in selected patients.

There are several possible links between SS and vaccines. Adjuvants may act by targeting the antigen-presenting cells via TLRs, NOD-like receptors (NLRs), RIG-I-like receptors and C-type lectin receptors. The downstream signaling leads to the activation of transcription factors such as NF-kB and IRF3, finally inducing the production of cytokines and chemokines involved in priming, expansion and polarization of the immune response. Aluminum, one of the most commonly used adjuvants, is able to trigger the activation of NLRP3 inflammasome signaling, leading to the production of pro-inflammatory cytokines (IL-1b, IL-18) via caspase-1 activation [13]. Recently investigated was the role of an aluminum-based adjuvant (alum) in the induction of SS-like disorder in the genetically susceptible NZM2758 female strain that develops reduced salivary gland function and sialadenitis following injection with incomplete Freund's adjuvant [14]. The alum-treated mice showed a persistent and significant reduction in salivary gland function, an increased submandibular salivary gland inflammation, and the production of antinuclear antibodies as compared to the controls treated with phosphate-buffered saline.

There is considerable evidence raising the possibility of vaccine-triggered autoimmunity, e.g., after A/California/7/2009/H1N1-like virus vaccine delivery in patients with SS, the mean titer of anti-SSA/Ro and anti-SSB/La antibodies increased [15]. Also reported was the case of a patient who developed sicca syndrome 3 months after vaccination with H1N1. In this specific case, rheumatoid factor (RF) and anti-SSA/Ro antibodies tested positive and a gland biopsy confirmed the diagnosis of SS [16]. Other vaccines have been suspected to trigger the onset of SS, one of which is hepatitis B. This vaccine has been associated with the development of clinical features of SS (dry mouth, dry eyes, arthralgia, fatigue) as well as laboratory findings of the disease (RF, antinuclear antibodies, and anti-SSA/

Table 1. Cases of SS possibly associated with silicone and vaccines exposure

Case reports	Case	Adjuvants	Time	Signs & symptoms	Autoantibodies	Histology	Genetic	Outcome
Sanchez-Roman et al., 1993	6/50 workers	**Silicone**	Ns	Dry mouth Dry eyes RP	Ns	Ns	Ns	Ns
Puisieux et al., 1994	3 cases among silicotic coal miners	**Silicone**	Ns	Dry mouth Dry eyes RP Arthralgia Purpura Polyneuritis	**In one case:** ANA Anti-SSA/Ro Anti-SSB/La **In one case:** Cryoglobulinemia	Ns	Ns	Ns
Orriols et al., 1997	28 years (M) Sicca syndrome (dental technician)	Silicone	5 years later	Dry eyes IP	Negative	Lymphocyte infiltrate Glandular sclerosis	Ns	Lung transplant
Toussirot et al., 2000	31 years (F)	Hepatitis B vaccine	1 month later	Arthralgia Fatigue Dry mouth Dry eyes	RF Ana Anti-SSA/Ro	Positive	HLA DRB1 P16/13	CCS and HCQ with benefit
Astudillo et al., 2003	72 years (M) (dental technician)	Silicone	3 months later	Dry mouth Dry eyes Arthralgia RP IP	ANA Anti-SSA/Ro	Positive	Ns	HCQ with benefit
Narváez et al., 2003	59 years (F)	BCG immunotherapy	Several weeks later	Dry eyes Dry mouth Swollen SG	Negative	Positive	HLA B27 Neg.	CCS with benefit
Toussirot et al. 2012	30 years (F)	H1N1 vaccine	3 months later	Arthralgia Dry mouth Dry eye	RF ANA Anti-SSA/Ro	Positive	HLA DRB1* 03, *15, DQB1 *02, *06	HCQ with benefit
Aykol et al., 2015	34 years (F)	Silicone	Soon after	Dry mouth Dry eye RP Leukopenia	ANA Anti-SSA/Ro Anti-SSB/La	Positive	Ns	HCQ with benefit

Ns = not specified, RP = Raynaud's phenomenon, RF = rheumatoid factor, ANA = antinuclear antibodies, IP = interstitial pneumonia, CCS = corticosteroids, HCQ = hydroxychloroquine, SG = salivary glands

Ro antibodies). Also in this case, the salivary gland biopsy supported the diagnosis of SS [17]. Some concerns related to BCG immunotherapy have been expressed as well. Specifically, the case of a patient developing SS following BCG exposure was described, and although autoantibodies tested negative the histology of lip biopsy confirmed the presence of inflammatory infiltrates [18].

SJÖGREN'S SYNDROME AND SILICONE

In 2003, the case of a male dental technician who developed SS, diagnosed according to a positive serology and lip biopsy after silicone exposure was illustrated [19]. A previous report described a similar case of sicca developing after silica exposure [20]. Moreover, SS development has been reported also after implantation of a silicone breast prosthesis. This occurred in a 34 year old female patient who developed leukopenia, dry mouth, dry eyes, and cyanosis of her fingers soon after silicone breast implantation [21]. She was diagnosed with SS and successfully treated with hydroxychloroquine. Six cases of SS were also described in coal miners and in workers from a factory producing scouring powder [22]. Puisieux et al. [23] reported three cases of SS in silicotic coal miners.

It is important to underline some cases of breast lymphomas, including non-Hodgkin lymphomas that occurred in women with compromised silicone breast implants. B cell lymphoma has also been described in subjects with other kinds of implants [24]. These lymphomas can be primary breast lymphomas, the majority (~90%) of B cell origin. The occurrence of anaplastic large cell lymphoma (ALCL), which accounts for less than 3% of newly diagnosed non-Hodgkin cases, has also been linked with breast implants. Following silicone exposure, ALK1-negative ALCL, a rare form of peripheral T cell lymphoma, has been also described. The hypothesized mechanisms for breast implant-associated lymphoma were recently addressed [25]. Silicone might trigger a chronic inflammation which leads a polyclonal B cell activation with local production of cytokines. The B cell oligoclonal and monoclonal expansion in infiltrated glands can in turn result in the development of a lymphoid malignancy. Although the transition from a chronic inflammatory condition to malignant lymphoma is a poorly understood multistep process, there is increasing evidence that chronic antigenic stimulation by an exoantigen or autoantigen plays an essential role in the development of SS associated lymph proliferation.

CONCLUSIONS

Whether certain adjuvants, by stimulating the immune system, may in turn provoke the full-blown picture of an autoimmune disease – such as SS – is still a matter of debate. Nonetheless, there are several shared features between ASIA syndrome and SS, and there is evidence of a number of SS cases following exposure to vaccines as well as to silicone. It should be borne in mind that, until recently, evidence strongly supported the idea that the benefits of vaccines largely outweigh the eventual risks of developing an autoimmune condition. Concerning silicone, larger cohorts will better define the existence of such an association. Clarifying these common mechanisms and addressing the key pathologic pathways will help us manage patients with SS and find innovative treatment strategies.

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