Lupus (2012) 21, 118–120
http://lup.sagepub.com

EDITORIAL

The spectrum of ASIA: 'Autoimmune (Auto-inflammatory) Syndrome induced by Adjuvants'

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Physicians are often puzzled by enigmatic medical conditions or the abrupt appearance of an immune-mediated disease. Such a story was recently presented to us by a young Sheikh. A Saudi Sheikh, who suffered at the age of 27 from joints pains, rash and serological evidence of anti-Ro antibodies, was diagnosed with probable systemic lupus erythematosus (SLE) at that time. He was treated with Plaquenil for a year, but as no signs of SLE were apparent, treatment was stopped and he remained disease free for the next 12 years. At the age of 39 years, 2 weeks after immunization with the flu vaccine, his disease reemerged. This time he presented with severe arthritis and pericarditis, which required treatment with high doses of steroids.

This patient's story illustrates the acceleration of an autoimmune or immune-mediated condition following exposure to external stimuli. During the past year a new syndrome was introduced and termed ASIA, 'Autoimmune (Auto-inflammatory) Syndrome induced by Adjuvants'.[1] This syndrome assembles a spectrum of immune-mediated diseases triggered by an adjuvant stimulus.[2–4] The use of medical adjuvants has become common practice and substances such as aluminum adjuvant are added to most human and animal vaccines, while the adjuvant silicone is extensively used for breast implants and cosmetic procedures. Furthermore, 'hidden adjuvants' such as infectious material or house molds have also been associated with different immune mediated conditions.[1,5] The adjuvant effect has been recognized for years, and is broadly utilized to enhance desired antigen-specific immune responses.[6] This effect is accomplished via mechanisms that impinge on both the innate and adaptive immune systems.[6–9] Formerly, adjuvants were thought to pose little or no independent threat. Alas, studies of animal models and humans demonstrated the ability of some of them to inflict autoimmunity and immune-mediated diseases by themselves.[2,10,11] Intriguingly, although exposure is common, adjuvant disease is relatively rare. It has been suggested that for a clinically overt adjuvant disease additional risk factors are required such as genetic susceptibilities or the co-exposure to other environmental factors.[1]

This special issue of *Lupus* is dedicated to ASIA and contains diverse articles from different geographical areas which provide a broad view of the clinical manifestations as well as the mechanisms related to the adjuvant effect.

The link between silicone, a synthetic polymer, and immune-mediated diseases has been accepted by the medical community and is one of the cornerstones of ASIA.[1,4] Nevertheless, the association between 'siliconosis' and systemic sclerosis remains controversial[4] and is reviewed herein by Lidar et al.[12] This review describes the mechanisms by which silicones mediate autoimmunity in general as well as the evidence for a casual association between this adjuvant and specific autoimmune diseases, such as systemic sclerosis. Following the same path Kivity et al.[13] present the case of a patient from the Middle East diagnosed with an overlap between morphea and eosinophilic fasciitis in association with breast implants. This silicone-related skin disease is within the spectrum of systemic sclerosis. From the other side of the globe Jara et al.[14] and Vera-Lastra et al.[15] report a patient with Still's disease after silicone implantation as well as a cohort of patients with severe local and systemic diseases following the illegal use of oil adjuvants for cosmetic purposes. The latter comprise of 50 patients, of which 41 were injected with mineral oil and 9 with other substances (e.g. iodide gadital, guyacol). Thirty of them presented with non-specific autoimmune disease and 20

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10.1177/0961203311429316

fulfilled the criteria for a defined autoimmune-rheumatic disease.

Another cornerstone of ASIA is the complex interaction between autoimmunity and adjuvanted vaccines. On the one hand vaccines are beneficial for the vast majority of subjects including those who suffer from autoimmune-rheumatic diseases as delineated in this issue by van Assen and Bijl.[16] On the other hand in a small minority of individuals vaccine can trigger the appearance of autoantibodies as documented by Vista et al.[17] and Perdan-Pirkmajer et al.[18] Moreover, a link between immunization and defined autoimmune diseases has been reported elsewhere and herein.[2] A plausible association between the flu vaccine and polymyalgia rheumatica is reported here by Soriano et al.[19] from Italy, and Soldevilla et al.[20] describe three patients diagnosed with SLE following immunization with the human papilloma vaccine from the Philippines. In addition, in a retrospective analysis Zafrir et al.[21] details common denominators among 93 American patients diagnosed with immune-mediated conditions following inoculation with hepatitis B vaccine. In this cohort although different autoimmune diseases were diagnosed, many manifestation were common to all patients and 86% of them fulfilled the criteria for ASIA. Of note, these cohorts signify only one side of the ASIA spectrum as they cope with distinct immune-mediated diseases while ASIA also comprises enigmatic and non-defined medical conditions. Two such conditions, the macrophagic myofasciitic syndrome and the Gulf War syndrome, are thus reviewed in this special issue by Gherardi and Authier[22] and Israeli.[23]

Although amassed clinical data has been presented in support of an association between adjuvants and immune-mediated diseases the proof of causality remains a challenge. Hence, in this issue two experimental models are portrayed, both of which prove the concept of autoimmunity induced by adjuvants. The induction of anti-phospholipid syndrome (APS) in two non-autoimmune prone mice strains, BALB/c and C57BL/6 via hyper-immunization with tetanus vaccine is reported by Dimitrijević et al.[24] APS, the Hughes syndrome, is characterized by obstetric morbidity and/or thrombosis and the presence of anti-phospholipid antibodies. In this model immunization with tetanus toxoid and different adjuvants (glycerol or aluminium hydroxide) or different adjuvant pretreatments (glycerol or CFA) induced pathogenic anti-phospholipid autoantibodies as well as fetal resorptions and reduced fecundity. In another model, NZBWF1 mice that are genetically prone to develop SLE were immunized with complete Freunds' adjuvant. Acceleration of SLE-like disease was observed as reported by Bassi et al.[25] In addition, the state of the art regarding oil adjuvants and autoimmunity is presented in this issue by Whitehouse,[26] while the various mechanisms of aluminium toxicity both in pediatric populations as in patients diagnosed with Crohn's disease are illustrated by Tomljenovic and Shaw[27] and Lerner.[28]

Taken together, this global view of ASIA probably represents only the tip of the iceberg. Encouraging physicians and patients to report adjuvant-related conditions will enable a better estimation of the true prevalence as well as the width of ASIA spectrum.[1,29] It seems that the role of adjuvants in the pathogenesis of immune-mediated diseases can no longer be ignored, and the medical community must look towards producing safer adjuvants. Studies that will address individual risk factors as well as different adjuvant-related ones are therefore urgently needed.

Meanwhile, reflecting on our patient, the young Sheikh, one might suggest that he was genetically prone to develop SLE and the exposure to the adjuvanted flu vaccine, simply triggered his malfunctioning immune system. Therefore, although immunization with the flu vaccine is considered safe for most SLE patients, for this particular patient, re-immunization should be considered with caution.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare no conflicts of interest expect for Y Shoenfeld, who has appeared in court for cases of vaccine injuries.

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