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Review

'ASIA' – Autoimmune/inflammatory syndrome induced by adjuvants

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ABSTRACT

The role of various environmental factors in the pathogenesis of immune mediated diseases is well established. Of which, factors entailing an immune adjuvant activity such as infectious agents, silicone, aluminium salts and others were associated with defined and non-defined immune mediated diseases both in animal models and in humans. In recent years, four conditions: siliconosis, the Gulf war syndrome (GWS), the macrophagic myofasciitis syndrome (MMF) and post-vaccination phenomena were linked with previous exposure to an adjuvant. Furthermore, these four diseases share a similar complex of signs and symptoms which further support a common denominator. Thus, we review herein the current data regarding the role of adjuvants in the pathogenesis of immune mediated diseases as well as the amassed data regarding each of these four conditions. Relating to the current knowledge we would like to suggest to include these comparable conditions under a common syndrome entitled **ASIA**, "Autoimmune (Auto-inflammatory) Syndrome Induced by Adjuvants".

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1. Introduction

In recent years four enigmatic medical conditions, defined by hyperactive immune responses were described. These conditions, namely siliconosis, the Gulf war syndrome (GWS), the macrophagic myofasciitis syndrome (MMF) and post-vaccination phenomena share a similar complex of signs and symptoms which suggest a common denominator to each one. Immune mediated conditions (i.e. autoimmune and auto-inflammatory diseases) are a leading cause of morbidity and mortality worldwide and their prevalence is rising in different geographical areas [1–3]. These geo-epidemiological changes can be explained by a complex of genetic and environmental factors [4,5]. Thus, a genetically susceptible subject may develop an autoimmune or auto-inflammatory disease (AI/AIFD) following exposure to a certain environmental factor [5–8]. Noteworthy, infections, toxins, and drugs were linked not only with the occurrence of immune mediated conditions but also with their clinical manifestations [7,8]. Environmental factors that comprise an immune **adjuvant** effect have been recognized for several decades. These adjuvants (i.e. silicone, alum, pristane, infectious components) were found to induce autoimmunity by themselves in different animal models and may possibly provoke AI/AIFD in

humans [9–13]. Exposure to these substances were documented in the four medical conditions conversed herein, suggesting that the common denominator to these syndromes is a trigger entailing adjuvant activity. Therefore, in this review we suggest to include these conditions under a common syndrome entitled ASIA, "Autoimmune (Auto-inflammatory) Syndrome Induced by Adjuvants".

1.1. Adjuvancy – the mechanisms

The term "adjuvant" derives from the Latin word *adjuvare*, meaning to aid. An immunologic adjuvant is a substance that enhances antigen-specific immune response preferably without triggering one on its own [13]. Adjuvants are commonly used in medicine to boost an immune response to treatments such as vaccination. The adjuvant effect is accomplished via several mechanisms that impinge on both the innate and adaptive immune systems [13–15]. Adjuvants increase innate immune responses by mimicking evolutionarily conserved molecules (e.g. bacterial cell walls, LPS, unmethylated CpG-DNA) and binding to Toll-like receptors (TLRs). Additionally, they augment the activities of dendritic cells (DCs), lymphocytes, macrophages and activate the intracellular Nalp3 inflammasome system [13]. Thus, adjuvants increase the local reaction to antigens (e.g. at the site of infection) and subsequently the release of chemokines and cytokines from T-helper and mast cells [13,16–18]. Currently the most widely used adjuvant in medicine is aluminium. Following an injection of aluminium salts (i.e. vaccination) danger-associated molecular patterns such as uric acid are released. High concentrations of uric acid form monosodium ureate crystals

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that are phagocytosed by resident cells and disrupt lysosomes functions. This results in the release of cathepsin B that can directly or indirectly activate the intracellular Nalp3 inflammasome system, and caspase-1. In doing so, aluminium stimulates the production and secretion of cytokines such as IL-1 β ; IL-18 and IL-33 [14].

Adjuvants also provide physical protection to antigens and aid in antigen translocation to the regional lymph nodes. This will ultimately enable a longer exposure of the immune system to the antigen, enhanced production and activation of both B and T cells and a more robust response. The adjuvant effect on the adaptive immune response is also mediated through activation of the Nalp3 inflammasome, which contribute to the induction of an adaptive T-helper 2 (TH2)-type responses, such as interleukin-4 (IL-4) and IgE production [13, 14, 6–18].

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 autoimmune diseases by themselves [13]. Perhaps the most studied adjuvant in this context is Tetramethylpentadecane (TMPD) known as pristane, which is capable of inducing a lupus-like disease in a murine model of systemic lupus erythematosus (SLE) [19,20]. In this model, similarly to the human disease, autoantibodies production and end-organ damage (i.e. renal disease) depend on interferon (IFN)-I receptor signaling pathway. Immunization of animals with pristane accelerated the production of IFN-I by monocytes *via* signaling through TLR-7 and the adapter protein MyD88 [19,20]. Immunization with another adjuvant, squalene, induce arthritis in rats and the production of SLE-associated autoantibodies in mice [19,21]. The adjuvant aluminium may be contained in immune complexes produced following vaccination [13,21].

1.2. The adjuvant role of infections

The multi facet associations between infectious agents and autoimmunity or auto-inflammatory conditions have been established and a number of mechanisms by which infectious agents can bring about such responses have been identified (i.e. molecular mimicry, epitope spreading, polyclonal activation and others) [8]. Yet, several questions regarding the interaction between infections and autoimmunity remain to be elucidated. For instance, unlike the classical example of a one-to-one alliance between streptococcal infection and rheumatic fever, the association of several infectious agents with a single autoimmune disease has recently been described [8]. On the other hand the same infectious agent (i.e. EBV) may relate to different systemic and organ specific autoimmune diseases [22]. Another misconception disclosed is the gap in time between exposure to infection and the diagnosis of autoimmune disease. Epidemiological evidence suggests that infectious exposure early in childhood may set the stage for the appearance of an autoimmune disease later in life [23,24]. This notion stands in agreement with the observation that autoimmunity (i.e. autoantibodies) appears years before a full blown autoimmune disease is diagnosed [25]. Recently, Noel Rose [26] suggested another mechanism, the adjuvant effect, by which infections may relate to autoimmunity in a broader sense.

Almost a century ago Jules Freund developed the complete Freund's adjuvant (CFA) that is a water and oil emulsion including killed mycobacteria. The importance of CFA in inducing diseases has been documented in many experimental models. For example, immunization of animals with thyroid antigen (thyroglobulin) and incomplete Freund's adjuvant, lacking the mycobacterial component, induced only the production of anti-thyroid antibody, whereas, immunization with the same antigen joined to CFA resulted in antibody production and inflammatory lesions in the thyroid [26]. Moreover, the addition of another microbial component (i.e.

microbial cell wall) to incomplete Freund's adjuvant resulted again in inducing a full blown experimental thyroiditis, supporting the idea of an adjuvant role to these microbial components. In another model of experimental autoimmune myocarditis the addition of the microbial component lypopolysaccharide to coxsackievirus B3 overcame a genetic barrier and induce autoimmune myocarditis in a strain genetically resistance to infection with coxsackievirus alone [26].

In other words, the activation of autoimmune mechanisms by infectious agents is common, yet the appearance of an autoimmune disease is not as widespread and apparently not always agent-specific. The adjuvant effect of microbial particles, namely the non-antigenic activation of the innate and regulatory immunity as well as the expression of various regulatory cytokines, may determine if an autoimmune response remains limited and harmless or evolve into a full blown disease.

1.3. Vaccines, post-vaccination phenomena and the adjuvant effect

Vaccines are one of the greatest achievements of modern medicine and are commonly and safely inoculated to human and animals worldwide. However, in rare occasions, similarly to infectious agents, vaccines can induce the appearances of autoantibodies, enigmatic inflammatory condition and overt autoimmune disease [9]. Of which, non-specific manifestations such as arthritis, neuronal damage, fatigue, encephalitis and vasculitis were frequently described [9,27]. These rare events were documented in case-reports, case series, studies as well as *via* the CDC vaccines adverse events reporting system, weeks and even months or years following vaccination [27,28]. As such, it was difficult if not impossible to delineate a causal relationship between vaccination and the diagnosis of defined and non-defined AI/AIFD. Nevertheless, for some vaccines such a causal link was noted. In 1976 an outbreak of Guillain-Barré syndrome (GBS) followed immunization with the "swine flu" vaccine [29,30]. Causal relationships have also been accepted for transverse myelitis following oral polio vaccine, arthritis following diphtheria-tetanus-pertussis (DTP) and measles-mumps-rubella (MMR) vaccine combinations and autoimmune thrombocytopenia after MMR [9]. In addition, a number of animal models enabled scientists a better way of studying the cause and effect link between vaccines and autoimmunity. Immunization of young dogs resulted in production of 9 different autoantibodies including lupus-associated ones [31]. In another study, specific vaccination protocols of diabetic prone newborn animals (i.e. NOD mice and BB rats) were associated with an increased incidence of diabetes [32]. Recently intra-peritoneal immunization of Salmon fish with oil-adjuvanted vaccines resulted in the production of autoantibodies (i.e. anti-nuclear, anti- β 2GPI, anti-ferritin and anti-salmon blood extracts antibodies) as well as autoimmune diseases documented by granulomatous diseases of the liver and peritoneum, thrombo-embolic disease and immune mediated glomerulonephritis [33].

The efficacy of most vaccines currently used either for humans or for animal immunization, depends on the presence of an adjuvant in conjunction with the infectious antigen [14]. Adjuvants increase the protective and lasting immune response to the infectious antigen and enable the decrement of antigen amount and thereby the production of a larger amounts of vaccines [13,34]. Alas, as was previously detailed adjuvants can also provoke an autoimmune response. Thus, in addition to the traditional adjuvants, newer more effective and perhaps safer adjuvants have been lately developed, such as the virosome, new oil based adjuvants (i.e. AS03 and MF59) and adjuvants that utilize Toll-like receptor signaling pathways (i.e. IC31 and AS04) [34].

Taking it all together, although the independent role of each vaccine ingredients as well as host risk factors are yet to be defined,

the accumulated data suggest the possibility of accelerated autoimmunity/inflammation following vaccination.

1.4. The macrophagic myofasciitis syndrome and the adjuvant alum

Perhaps the most evaluated post-vaccination condition is the macrophagic myofasciitis syndrome (MMF), in which a causal link was clearly delineated. MMF is a rare immune mediated condition first reported in France by Gherardi et al. [35]. It is caused by deposition of aluminium, used to adjuvant different vaccines, which bring about an immune mediated muscle disease. MMF characterizes by systemic signs and symptoms as well as local active lesion at the site of inoculation [36,37]. Systemic manifestations include myalgias, arthralgia, marked asthenia, muscle weakness, chronic fatigue, fever and in some cases the appearance of a demyelinating disorder. Additionally, elevated creatine kinase (CK) and erythrocyte sedimentation rate as well as the appearance of autoantibodies, and myopathic EMG changes have also been documented [35–38]. The local lesion of MMF was found to result from persistence of aluminium adjuvant at the site of inoculation months and even 8–10 years following immunization [39]. Muscle biopsy reveal infiltration of large PAS-positive, MHC-1- positive macrophages and CD8 T-cells, in the absence of muscle fiber damage. At electron microscopy, these macrophages enclose cytoplasmic crystal material representing aluminium hydroxide [13,36]. Intriguingly, a discrepancy exists between the wide application of aluminium hydroxide and the rarity of MMF. This inconsistency was resolved by the observations that MMF might appear mainly in genetically susceptible subjects carrying the HLA-DRB1*01. This connection was first described in identical twin sisters diagnosed with MMF. In addition it was detected in 66% of 9 patients with MMF compared with 17% of 230 controls suggesting an odds ratio of 9.8 (95% confidence interval 2.0–62.2) [40]. Thus, lending support to the idea that in a minority of genetically prone patients aluminium may induce this syndrome.

1.5. The Gulf war syndrome

Another syndrome implicated to the adjuvant effect is the Gulf war syndrome (GWS). It is portrayed by chronic fatigue and other clinical manifestations that share many similarities with MMF. Multiple vaccinations performed over a short period of time were suggested to be the cause of this syndrome. Of note, during the Gulf war, the veterans' vaccination protocol included the anthrax vaccine, which was administered in a six-shot regimen and was adjuvanted by aluminium hydroxide and squalene [13]. Previously both infectious agents and vaccines have been reported to precede the development of chronic fatigue syndrome (CFS) and fibromyalgia, and a role for Th-2 mediated immune response was suggested [12,41,42]. Therefore, it was postulated that the GWS is the result of the adjuvant effect that induced a chronic Th-2 immune response [12]. Furthermore, Asa et al. [43] sought to find if the presence of antibodies to the adjuvant squalene correlated with the diagnosis of GWS. In a relatively large study of 144 Gulf war-era veterans 95% of overtly ill deployed GWS patients had antibodies to squalene and **100%** of GWS patients immunized for service in Desert Shield who did not deploy, but had the same signs and symptoms as those who did deploy, had antibodies to squalene. In contrast, none of the control groups that incorporated patients with autoimmune diseases, healthy controls and Persian Gulf veteran's not showing signs and symptoms of GWS had antibodies to squalene. Thus, although the pathogenesis of GWS is under scrutiny, the data assembled at this time highlight the possible role of adjuvants in this syndrome.

1.6. Siliconosis and the adjuvant disease

Last but not least, immune mediated phenomena and autoimmune diseases following exposure to silicone (i.e. breast implant), had been an issue of debate for many years. Silicone was previously considered to be an inert material, but apparently, like other adjuvants, it is capable of inducing autoimmune-like phenomena termed in the early 1990s "the adjuvant disease" [44]. At that time various cases of defined connective tissue diseases were described in patients with silicone implants. Moreover, in a large cohort study, based on self-reported symptoms of approximately 11800 implanted women a relative risk of 1.25 (95% CI: 1.08–1.41) for all defined connective tissue diseases was suggested [45]. However, in 2000, a meta-analysis published by Janowsky et al [46] that did not include the former study, concluded that the risk of defined connective tissue diseases following silicone breast implantation was only 0.80 (95% CI: 0.62–1.04).

Unlike the controversy regarding defined autoimmune diseases, a relationship between silicone implants and a collection of symptoms that do not fulfill any diagnostic criteria for a defined connective tissue disease was reported by several groups suggesting that indeed a non-defined syndrome may appear following exposure to silicone. Vasey et al. [47] concluded that statistically significant increases in many signs and symptoms such as body ache, joints pain, myalgia, fatigue, impaired cognition and others, were associated with silicone breast implants. In another large study Fryzek et al. [48] found a statistically significant increase in 16 of 28 investigated symptoms in a group of 1546 patients with silicone breast implants compared to a group of 2496 women who underwent reduction mammoplasties. Again, these manifestations bear a resemblance to MMF and GWS and satisfied several criteria for fibromyalgia and chronic fatigue syndrome. The latter are severely disabling conditions that have a number of prominent symptoms in common and coincide in many individuals. While a little is known of their etiology, both conditions are characterized by an aberrant immune response. Recently we and others suggested a role for an adjuvant mechanism in the pathogenesis of these conditions namely, silicone [12] and/or aluminium-containing adjuvants in vaccines [12,37]. This stands in agreement with the FDA's finding that there is a statistically significant link between fibromyalgia and ruptured silicone gel implants [49]. The analysis of this specific set of manifestations led to the definition of a new entity termed "siliconosis" which include the presence of body

Table 1

The prevalence of clinical manifestations: MMF, Silicone related disease; GWS and post-vaccination events.

Symptoms	MMF N = 250	Silicone N = 100	GWS N = 4600	Post Vaccines N = 30000
Myalgias/myopathy/muscle weakness	+++	+++	+	+
Arthralgias/arthritis	+++	+++	++	+
Chronic fatigue/sleep disturbances	+++	+++	+++	+
Neurological/cognitive impairments	+	++	++	+
Fever	+	NR	NR	+
Gastrointestinal	+	NR	+	+
Respiratory	NR	NR	+	+
Skin		+	+	+
Diagnosis of defined autoimmune disease	+	+	NR	+/-
Antibodies	NR	+	+	NR
Increased ESR	++	NR	NR	+
References	8, 21	22	11, 23	24

The prevalence of signs and symptoms was defined as (+) if reported in <30% of subjects, (++) in 30–60% and (+++) if present in more than >60% of subjects. MS – multiple sclerosis; NR – not reported.

Table 2
Suggested criteria for the diagnosis of 'ASIA'.

<p>Major Criteria:</p> <ul style="list-style-type: none"> • Exposure to an external stimuli (Infection, vaccine, silicone, adjuvant) prior to clinical manifestations. • The appearance of 'typical' clinical manifestations: <ul style="list-style-type: none"> – Myalgia, Myositis or muscle weakness – Arthralgia and/or arthritis – Chronic fatigue, un-refreshing sleep or sleep disturbances – Neurological manifestations (especially associated with demyelination) – Cognitive impairment, memory loss – Pyrexia, dry mouth • Removal of inciting agent induces improvement • Typical biopsy of involved organs <p>Minor Criteria:</p> <ul style="list-style-type: none"> • The appearance of autoantibodies or antibodies directed at the suspected adjuvant • Other clinical manifestations (i.e. irritable bowel syn.) • Specific HLA (i.e. HLA DRB1, HLA DQB1) • Evolvement of an autoimmune disease (i.e. MS, SSc)

ache, abnormal fatigue, impaired cognition, depression, dry eyes, dry mouth, skin abnormalities, paresthesia, swollen and tender axillary glands, unexplained fever, hair loss, headache and morning stiffness [47–50]. Hence, it seems that the link between silicone and autoimmunity should not be limited by the constraints of defined diseases, but rather relate to the relatively prevalent non-defined symptoms.

1.7. ASIA – autoimmune/auto-inflammatory syndrome induced by adjuvant: a new syndrome to be defined

These enigmatic, nevertheless prominent clinical signs and symptoms are common to the four conditions discussed in this review, and coincide in many individuals diagnosed with either 'siliconosis' MMF, GWS or post-vaccination events (Table 1). Additionally, in up to 35% of patients' autoimmunity (i.e. autoantibodies) or an overt autoimmune disease was described.

Furthermore, a common denominator to these four conditions is presently suggested that is the exposure to a component that comprises an adjuvant effect. One might suggest that similarly to animal models, and the genetic link observed in MMF, the adjuvant effect persuade the appearance of these conditions only in subjects who are genetically susceptible. Another possible explanation, that may overcome genetic barriers, is the co-exposure to more than one trigger such as the exposure to another deleterious environmental factor (i.e. infectious agent) or co-exposure to more than one adjuvant [12,51].

Taking it all together, we suggest that these four somehow enigmatic conditions: siliconosis, MMF, GWS and post-vaccination phenomena that share clinical and pathogenic resemblances will be included under a common syndrome entitled the "Autoimmune (Auto-inflammatory) Syndrome Induced by Adjuvants" (ASIA). We further propose several major and minor criteria, that although require further validation may aid in the diagnosis of this newly defined syndrome (Table 2).

The amassed data regarding each condition may enable us a spacious view of the immune responses to environmental adjuvants, as well as better definition and diagnosis of these conditions. Moreover unraveling the pathogenesis of this newly defined syndrome may facilitate the search for preventive and therapeutic interventions.

Disclosure

Yehuda Shoenfeld appeared in court on the issue of vaccine induced autoimmune conditions.

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