ASIA Syndrome

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Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) was first introduced in 2011 by Shoenfeld et al. and encompasses a cluster of related immune mediated diseases, which develop among genetically prone individuals as a result of adjuvant agent exposure.

Keywords: autoimmune diseases ; ASIA syndrome ; autoimmune/inflammatory syndrome induced by adjuvants ; adjuvants ; autoantibodies ; silicone

1. Introduction

Autoimmune/Inflammatory syndrome induced by adjuvants (ASIA) was first introduced in 2011 by Shoenfeld et al. [1] and encompasses a cluster of immune mediated diseases, which are likely to develop among genetically predisposed individuals after the exposure to an adjuvant. These conditions share several clinical aspects with the possible appearance of autoantibodies, and trend to improve once the inciting agent is removed [2]. Clustering of autoimmune diseases (AID) in families is well recognized, supporting a common genetic background [3]. It is necessary that external environmental factors (infectious agents, dust, vaccines, etc.) or other adjuvant agents triggering immune activity (dust, silicone, aluminum salts, etc.) cooperate on this favorable genetically determined background, in order to promote the disease onset [4][5][6][7][8][9]. Notably, loci in the human leukocyte antigen (HLA), which have been shown to be associated with the development of AID have been suggested to be associated with the classical ASIA syndrome conditions [3][10]. Further, adjuvants influence both the innate and adaptive arms of the immune system via assorted mechanisms, encouraging the initiation and perpetuation of immune response by the activation of pattern recognition receptors. Nevertheless, enhanced immunogenicity might lead to reactogenicity in a process that does not always begin involving pathological stimulation [11].

2. Classical Examples of the ASIA Syndrome

The establishment of the ASIA concept in 2011, has allowed to clarify the different pathways leading to the development of assorted autoimmune conditions considered so far to be “enigmatic”. Under the light of the recent discoveries, also supported by our own research results, disorders such as sarcoidosis, Sjögren syndrome (SS), undifferentiated connective tissue disease (UCTD), silicone implants incompatibility syndrome (mainly associated with silicone breast implants), and irAEs were able to be segregated as classical examples of the ASIA syndrome concept.

2.1. Sarcoidosis

Sarcoidosis is a systemic granulomatosis disorder of unknown etiology characterized by the formation of immune granulomas in various organs, mainly the lungs and the lymphatic system [12]. Studies have hypothesized that sarcoidosis might be the result of an exaggerated granulomatous reaction occurring after the exposure of a genetically prone individual to an unidentified antigen, that triggers a Th1-type cellular immune response leading to the formation of granulomas [13]. The hyperstimulation of the immune system is most probably prompted by an inorganic material, infection, environmental stimuli and/or autoantigens [14].

Several genome wide association studies have demonstrated that both HLA and non-HLA alleles are associated with the development of sarcoidosis and with disease phenotype [15] .

2.2. Silicone Implant Incompatibility Syndrome

Women with silicone-related complaints due to SBIs have been included in the classical models of ASIA syndrome. The silicone present in the breast implants represent an external non-self, chronic stimulus that may lead to hyperstimulation of the immune system in genetically predisposed individuals, appearance of non-specific subjective clinical

manifestations, and autoantibody production, which might precede the development of autoimmune diseases, and most rarely lymphoma.

Silicone injections and the subsequent use of SBIs for breast reconstruction and breast augmentation have been reported since 1960's [16][17][18]. The safety of silicone breast implants has stirred an intense debate, concerning their potential for induction of autoimmunity and lymphoma [19][20][21][22][23][24][25][26][27][28]. The expression of HLA-DRB1 and HLA-DQ alleles in patients with SBIs can be related with the development of autoimmune symptoms [29][30][31][32]. Several plausible mechanisms have been proposed to explain the link between SBIs and autoimmune phenomena, as it has been shown in animal model studies. For example, injection of silicone-gel in NZB mice has led to the induction of proteinuria and autoimmune hemolytic anemia, whereas implantation of silicone-gel or silicone oil in MRL lpr/lpr mice has led to the increase of anti-ds-DNA antibodies [33][34][35]. We have previously shown that silicone can trigger UCTD, SSc and fibromyalgia [22][35][36]. Moreover, in a large population-based study, we have recently demonstrated an association between SBIs and the presence of autoimmune/rheumatic disorders such as SS, SSc, and sarcoidosis [37]. Furthermore, we have reported an increased production of a broad range of autoantibodies in asymptomatic and symptomatic women with SBIs [38]. These autoantibodies may predict and precede the development of autoimmune disease in these women. The complex link between SBIs and autoimmunity can be illustrated by the concept of ASIA syndrome [1][23][24][39].

2.3. Sjögren's Syndrome

SS is a chronic systemic autoimmune inflammatory condition primarily involving the exocrine glands in which both genetic and environmental factors play a pathogenic role. Infections represent the most prominent trigger of disease [40] leading to a dysregulated immune response largely driven by an overexpression of type I interferons, B cell proliferation, aberrant cytokine production, and tissue infiltration. Recent evidence suggests that several agents may act as adjuvants in determining such abnormal immune response possibly contributing to the development of SS [41][42]. Vaccinations, which should follow a recommended schedule in patients with autoimmune diseases including patients with SS, should preferably be administered during quiescent phases of the diseases due to the possibility to trigger a disease flare [43][44] and for same reason live attenuated vaccines should be avoided. Some studies suggested that SS onset can be associated with specific vaccines, still a temporal rather than a causal association should always be considered [45][46][47]. Nonetheless, it was shown that, in patients with primary SS, the A/California/7/2009/H1N1-like virus vaccination lead to a significant increase in the mean levels of anti-SSA/Ro and anti-SSB/La antibodies after 1-year of follow-up [48]. Alum, an aluminium-based adjuvant, was able to induce a Sjögren's syndrome-like disease in an experimental New Zealand Mixed (NZM) 2758 strain of mouse in which ANA positivity, chronic salivary gland dysfunction and lymphocytic infiltrates within the salivary glands was observed.

2.4. Undifferentiated Connective Tissue Disease

Several conditions in the field of autoimmunity are characterized by non-specific signs and symptoms that cannot be classified into a definite nosological entity according to international criteria. An increasing number of patients have been referred to rheumatology consultation for chronic fatigue, myalgia, muscle weakness, arthralgia/arthritis, and interstitial lung disease [49][50]. The term 'undifferentiated' used to describe all these conditions not only reflects an undefined clinical picture but also a poor knowledge of the underlying etiopathogenic mechanisms. UCTD is a term that encompasses a broad spectrum of conditions characterized by signs, symptoms and laboratory features that are suggestive of systemic autoimmune diseases (SADs) [51]. Such a kaleidoscope of clinical presentations poses the question whether the UCTD can be considered as a distinct entity or may be early forms of definite SAD, which is the reason why the classification criteria for UCTD are still a work in progress [52].

The induction and perpetuation of autoimmunity is a complex process that requires the interaction between the genetic background and the environment. Environmental factors are gaining increasing attention in the pathogenesis of UCTD. Similar to ASIA [95,96], UCTD is an autoimmune condition characterized by non-specific signs and symptoms, alluding to the idea that the exposure to adjuvants can be a trigger of UCTD. To investigate the possible environmental triggers of UCTD, a case–control study on the exposure to different adjuvants in 92 patients with UCTD and in 92 age and sex-matched controls was performed in Italy [36]. Exposure to several adjuvants prior to UCTD onset (during the 10 years before diagnosis) was found to be significantly more frequent than healthy controls, suggesting that nearly half of UCTD patients in our cohort might fall within the spectrum of ASIA. Interestingly, patients exposed to major adjuvants (vaccines containing adjuvants or silicone implants) displayed the typical features of ASIA, particularly fibromyalgia symptoms. The association between vaccinations and autoimmune phenomena has been described as either simple appearance of autoantibodies or as a full-blown autoimmune disease [53][54].

2.5. Immune-related Adverse Events

The irAEs are autoimmune complications of check-point inhibitors (CPI) therapy used in cancer treatment. The main difference of IrAEs in comparison with AID is a lack of the chronicity [55]. It is one of the ASIA classical example where the external stimuli are known, and its pathogenesis is well described. In this case “adjuvants” are monoclonal antibodies, that inhibit a receptor associated with cytotoxic T lymphocytes (CTLA-4), a programmed cell death receptor-1 (PD-1), and its main ligand PD-L1. The blockade of control points CTLA-4 and PD-1 reduces the prevention against autorecognition by lymphocytes and contributes to activation of CD-8+ and CD4+ T cells against cancer cells. This overstimulation of immune system breaks the auto-tolerance and leads to autoimmune reactions [56]. According to clinical trials irAES develop up to 90% of patients treated with an anti-CTLA-4 antibody and 70% of patients treated with an PD-1/PD-L1 antibody [57][58]. The median onset is 3–6 months after the start of treatment. However, late adverse events, which occur after a year or more, are also documented [59]. In mild cases the symptoms might disappear by its own or after termination of CPI exposure, but severe irAEs needs to be managed with immune-modulatory medications, such as steroids, biological therapy, or cytostatic drugs [60][61][62]. In addition, the characteristic ASIA symptoms can occur in patients who have developed musculoskeletal toxicities, which are found in 2-12% of cases and can manifest as inflammatory arthritis, myalgia, myositis, and syndromes similar to polymyalgia [63]. Fever is a common complication of immunotherapy. In patients with non-small cell lung cancer, fever was associated with a low level of progression free survival[64].

3. Conclusions

ASIA syndrome encompasses various autoimmune conditions that flourish under the influence of triggering factors among predisposed individuals, which provoke immunological reactions characteristic of autoimmune diseases. Conditions for which etiology is so far beyond comprehension, such as sarcoidosis, Sjögren’s syndrome, UCTD, silicone implant incompatibility syndrome, and immune adverse related events, represent classical examples of the ASIA syndrome. The described major (clinical) and minor (immunogenetic) diagnostic criteria enable us to assume the autoimmune nature of inflammation seen in these diseases. The harmful role of adjuvants has already been recognized in the scientific community, and although vaccines contain adjuvants, it is extremely important to highlight that general benefits of vaccination far outweigh the risk of immune-related side effects. In this manner, efforts should be made in order to understand, clarify, and raise the awareness of clinicians regarding the ASIA concept, for a better discernment between the adjuvant-induced pathologies and their prevention among genetically predisposed individuals. They could test for specific genetic markers (largely unknown) for every vaccination. Nevertheless, some open questions remain and should be addressed in future studies, such as “Why is there autonomic dysfunction and neuropathy in women with SBIs as apparent in the production of autoantibodies against specific receptors of the autonomic nervous system and SFN.

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