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Autoimmune / inflammatory syndrome induced by adjuvants (ASIA) – variety of symptoms

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Abstract Introduction

The autoimmune / inflammatory syndrome induced by adjuvants (ASIA) has been described by Shoenfeld and Agon-Levin (in 2011). It is an autoimmune / auto-inflammatory disease caused by adjuvants. Adjuvants are substances able to induce autoimmunity via various mechanisms such as a change in the host immune system, polyclonal activation of B cells,

effects on cellular immunity, immunoregulatory cells, antibodies induced by viruses or acceleration of molecular mimicry.

The aim

The purpose of the work was to congregate information about ASIA useful in medical practice.

State of knowledge

The ASIA syndrome can be diagnosed when two main or one main and two smaller criteria are fulfilled.

The main criteria:

External stimulus exposure

Muscle pains, muscle inflammation or muscle weakness

Arthralgia and / or arthritis

Chronic fatigue, sleep without rest or sleep disorder

Neurological symptoms

Impaired cognitive function, memory loss

Fever, dry mouth

Removal of the inducing factor induces an improvement

Result of organ biopsy

Smaller criteria:

Other clinical signs (irritable bowel syndrome)

Presence of HLA antigens (ie HLA DRB1, HLA DQB1)

Development of autoimmune disease (multiple sclerosis, systemic sclerosis).

ASIA syndrome may occur after implantation of silicone breast implants and cause various complications of other pain, fever and skin changes.

Conclusion

Autoimmune / auto-inflammatory disorders can be caused by silicone implants and vaccine adjuvants: they include the presence of autoantibodies, muscle and joint pain, lupus-like symptoms and hardened-like symptoms.

Key words: ASIA; adjuvants; autoimmune syndrome

Introduction

The autoimmune / inflammatory syndrome induced by adjuvants (ASIA) has been described by Shoenfeld and Agon-Levin (in 2011). It is an autoimmune / auto-inflammatory disease caused by adjuvants. Adjuvants are substances able to induce autoimmunity via various mechanisms such as a change in the host immune system, polyclonal activation of B cells, effects on cellular immunity, immunoregulatory cells, antibodies induced by viruses or acceleration of molecular mimicry [1]. They are used as components of vaccines.

Excessive immune response is largely associated with genetic predispositions and environmental factors to which the patient is exposed. Substances with adjuvant immune

effects such as silicone, aluminum salts and Freund's adjuvant contained in vaccines, as well as mineral oils, collagen and hyaluronic acid used in cosmetic fillers and implants, have been linked to the occurrence and development of autoimmune diseases [2] such as: rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SS), Sjögren's syndrome (SjS), eosinophilic fasciitis (EF), polymyositis and chronic fatigue syndrome (CFS) [1].

According to Watad et al., the average age of these diseases in exposed individuals was 37 years. The average time lag between exposure to adjuvant incentives and the development of autoimmune disorders was on average 16.8 months (from 3 days to 5 years). Patients usually reported joint pain, muscle aches and chronic fatigue [2]. ASIA was associated with the main four medical disease: siliconosis, Gulf War Syndrome (GWS), macrophagic myofasciitis (MMF) and post-vaccination reactions [3].

Gulf War Syndrome (GWS) includes chronic fatigue and other clinical symptoms that have many similarities with other units associated with ASIA. The reason for this unit was the multiple vaccinations made in a short period of time for soldiers participating in the war. Currently, research on the pathogenesis of GWS is in progress. However, the possible role of adjuvants is underlined.

Macrophagic myofasciitis (MMF) is a rare immune disorder caused by the deposition of aluminum, used as an adjuvant in various vaccines. MMF is characterized by systemic symptoms that include muscle pain, arthralgia, asthenia, muscle weakness, chronic fatigue, fever, and in some cases demyelinating disorders. It was found that local damage to MMF results from the presence of an aluminum adjuvant at the site of vaccination up to 8-10 years after immunization. The muscle biopsy shows the infiltration of PAS positive, MHC-1 positive and CD8 T-positive macrophages, with no damage to the muscle fibers. However, there is a disproportion between common use of aluminum hydroxide and the rarity of MMF. This is due to the fact that MMF may appear mainly in genetically-prone individuals, and in the rest of the population, aluminum hydroxide is immunologically inert. [5]

The purpose of the research work

The purpose of the work was to congregate information about ASIA useful in medical practice.

Materials and methods

The article was based on scientific publications in the Pubmed database. The database was searched on 12 December 2018 using the phrases 'ASIA', 'adjuvants', 'autoimmune syndrome induced by adjuvants'. After reading the titles of found articles, 25 articles were selected. After the pre-analysis of the abstracts, 13 full-text works were selected to prepare the article.

Results and discussion

The ASIA syndrome can be diagnosed when two main or one main and two smaller criteria are fulfilled.

The main criteria:

- External stimulus exposure (infection, vaccine, silicone, adjuvant) before the onset of clinical symptoms
- Muscle pains, muscle inflammation or muscle weakness
- Arthralgia and / or arthritis
- Chronic fatigue, sleep without rest or sleep disorder
- Neurological symptoms (especially associated with demyelination)
- Impaired cognitive function, memory loss
- Fever, dry mouth
- Removal of the inducing factor induces an improvement
- Result of organ biopsy

Smaller criteria:

- Presence of autoantibodies or antibodies directed against suspected adjuvants
- Other clinical signs (irritable bowel syndrome)
- Presence of HLA antigens (ie HLA DRB1, HLA DQB1)
- Development of autoimmune disease (multiple sclerosis, systemic sclerosis) [4].

Threats that appear after breast implantations

Breast implants are made of silicones, which are a group of synthetic polymers. Three common forms of silicone are: elastomer (silicone), liquid and gel. After the implant is implanted, a fibrous encasement with myofibroblasts, macrophages and multinuclear cells surrounding the implant is formed around it. In the case of rupture of an implanted silicone gel prosthesis and leakage of contents, it is stated silicone granuloma, local inflammation and regional lymphadenopathy. Patients with immunological reactions have elevated IgG and anti-silicone antibodies. Allergic reactions to silicone are possible. Even if the implant is not broken, the diffusion of silicon through the envelope into the surrounding tissues ("bleeding") can be a complication. [4]

After more than half a century, the safety of silicone breast implants is a matter of debate around the world. In 1992, the Food and Drug Administration (FDA) limited the use of silicone breast implant in the US due to cases of disease associated with fibromyalgia, systemic symptoms and autoimmunity. In 2000, Janowsky et al. [6] conducted research on this subject and concluded that silicone breast implants can be considered safe. However, in this meta-analysis, 10,830 patients were excluded due to the fact that the complaints of these patients were "reported by the patients themselves". If this research weren't skip, the relative risk of connective tissue disease would increase from insignificant to significant worth 1.3. This meta-analysis included only the development of a defined connective tissue disease, not the development of ASIA or other disease states [2].

In 1964, Miyoshi et al. described a case of two patients which developed connective tissue disease several years after implantation of the breast implant. Since then, exposure to

silicone has been linked to several autoimmune diseases such as multiple sclerosis, chronic fatigue syndrome, rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, mixed connective tissue disease, as well as other autoimmune diseases developing in women who have undergone implantation of silicone breast implants [4].

The variety of symptoms and conditions that may develop after implantation can be illustrated by several clinical cases, which will be presented below.

An interesting case of ASIA syndrome occurred in a 23-year-old Brazilian. Three years earlier, the woman underwent breast augmentation surgery using retroglycular polyurethane-silicone gel dentures. The woman did not have any allergies, in the past she did not take any drugs chronically. The surgery itself went without complications and for 3 years the patient did not notice any changes and avoided exposure to UV rays around the cleavage. After 3 years at the time of the planned check-up, the patient reported the appearance of a recently-erythematous rash around the breast, which gradually increased. Physical examination revealed no abnormalities except for bilateral erythematous skin eruptions. There was no contracture of the nipples or any other abnormalities. The initial suspicion was allergic contact dermatitis and for diagnostic purposes an allergic patch test was carried out, the result of which was negative. In addition, laboratory tests were performed and the presence of antinuclear antibodies in the titer of 1: 640 was found. Also in the diagnostic imaging, no abnormalities were found. In a biopsy examination of skin with erythematous changes on the left breast, fragments of the thinned epidermis, focal hyperkeratosis, follicular degeneration and thickening of the epithelial basement membrane were indicated. The perivascular infiltration of lymphocytes was found in papillary and superficial dermis. Based on the clinical picture and the results obtained, the patient was diagnosed with ASIA syndrome - with lupus-like symptoms. Hydroxychloroquine treatment at 400 mg daily was started. After 3 months there was an improvement, and after 6 months no erythematous changes in the skin were found. The woman still receives hydroxychloroquine and remains asymptomatic after 2 years. The described case is rare, since the patient only needed immunosuppressive therapy without removing the implant, which was required in all cases previously described in the literature. What's more, after 2 years of follow-up, there was no recurrence of symptoms. This suggests that silicone is a weak antigenic material and can be preserved if symptoms occur with adequate pharmacological intervention [7].

Another example is the 55-year-old Russian woman who reported to the doctor due to the progressive skin tension of the hands, feet and face during the last year. The patient smoked cigarettes for 15 years and underwent breast enlargement surgery with silicone implants 15 years earlier. After 10 years without any symptoms, the patient experienced Raynaud's symptoms, and after another 5 years there were additional symptoms: pain in the wrists and shoulders, heartburn and difficulty in swallowing, mild exercise dyspnoea and swelling of the fingers and toes. In the physical examination, the patient was observed numerous teleangiectasias on the skin of the hands and feet as well as the fibrosis of the skin. Laboratory tests revealed positive anti-centromere antibody, chest X-ray showed interstitial pulmonary fibrosis, and capillaroscopy showed active sclerosing angiopathy. The patient's therapy included intravenous cyclophosphamide administration followed by a maintenance treatment with methotrexate at a dose of 10 mg / week. Two years later, the patient experienced pain, redness and swelling of the left breast. A purulent infection of the left breast was diagnosed. The breast implant was removed and an intravenous

antibacterial therapy was administered. The patient took methotrexate, vitamin C and E. There were significant swelling of her fingers and numerous new teleangiectasias of her hands. [8]

It is important that more than 80 women with silicone breast implants have been diagnosed with anaplastic large B-cell lymphoma. One such case was a 48-year-old Caucasian woman who was admitted to the hospital with fever, splenomegaly and physical fatigue. In addition, she was diagnosed with pancytopenia and hyperferritemia. There were also symptoms of altered sensory sensation, hemiparesis and aphasia. After dexamethasone administration there was improvement, but after 3 days again high fever appeared again, which did not decrease after administration of immunoglobins and cyclosporin A. Histological examination showed reaction to foreign body, which suggested ASIA syndrome. The study also made it possible to diagnose large B-cell lymphoma. Silicone breast implants were recognized as a trigger factor for the development of cancer and decided to remove them. Four years earlier, the woman was diagnosed with breast cancer and underwent mastectomy. Then she underwent breast reconstruction surgery using silicone implants. After some time, the reduction of the left breast was performed, as well as lipofiling of the bust [9].

It was shown that silicone gel in black mice in New Zealand contributes to the development of autoimmune diseases, whereas in BALB7cAnPt mice it does not cause such an effect. On this basis, a hypothesis was put forward that silicone may play a similar role in a small number of women with genetic predisposition.

According to studies conducted in New Zealand, people with HLA-DRB1 * 11, HLA-DQB1 * 03- are more likely to have B-cell lymphoma, haematological tumors, non-granulomatous lymphomas, acute and chronic lymphoblastic leukemia and hairy cell leukemia, so they are more vulnerable after implantation. A case of a 48-year-old female with ASIA was described. Her uncle died at the age of 43 from acute leukocyte leukemia, which may be related to these alleles in him, as well as in his family. These genes are also associated with autoimmune diseases.

Non-Hodkin breast lymphoma is extremely rare, so this lymphoma in women with breast implants raises some suspicions about the relationship between the disease and the implants. The lack of strong evidence for the causative role of silicone breast implants reflects the rarity of this disease [9].

Another case of adverse reaction after exposure to adjuvants is illustrated by the case of a 37-year-old transgender Brazilian with implanted silicone breast implants and buttocks, as well as injected subcutaneous loose silicone fillers in the mouth, wrist, breast area, axillary areas, knees, hips, thighs, groins and arms 14 years earlier. She reported with fever, abdominal pain, night sweating, dry cough, weight loss from one month and asthenia. The inflammatory syndrome in the course of normal inflammatory response (IRIS) occurred at the same time with biopsy confirmed granulomatous lesions that were associated with long-term silicone subcutaneous implants.

The distribution of skin lesions was related to sites of previous subcutaneous injection and leakage of silicone from a broken right breast prosthesis. No skin changes observed outside these locations. Silicone-related infections or drug toxicity were unlikely to be the

cause of the disease, and the entire clinical picture subsided after using corticosteroids without removing any silicone implant [3].

The effects of implant placement can be very different. These effects may also include pleurisy and pericarditis, as was the case of a 60-year-old Japanese woman who was admitted to the hospital due to a 7-week prevalence of fever and chest pain on the left side. There was no cough, sputum, rash, hypersensitivity to light, joint pain or Raynaud's symptom. The patient had a funneling chest. She underwent breast augmentation surgery. No signs of inflammation were found on the chest wall, but the possibility of reacting to silicone implants was considered and surgery was performed to remove them. It was found intraoperatively that the right breast implant is cracked and a leak of silicone was noted. This case raises 2 important clinical problems. First, the implant fracture caused pleurisy and pericarditis, and pleurisy occurred on the opposite side to the rupture. Secondly, pleurisy and pericarditis have been completely cured by removing the silicone implants themselves [10]. In this patient, there were symptoms associated with, among others, a broken implant, however, it should be noted that 27% of patients with broken silicone implants are not complaining about any local symptoms [11].

There are hypotheses about the effect of vitamin D on the development of autoantibodies in patients with ASIA. Vitamin D is a potent regulator of the immune system, and its deficiency contributes to the overactivity of B-cells. Several mechanisms have been described where vitamin D is a regulator for the innate and adaptive immune system. First, the cells of the immune system turned out to be the direct targets of vitamin D metabolites. Second, many immune cells contain enzymes in the cytochrome P family (CYP) and are thus able to convert 25- (OH) D to calcitriol (the biologically active form of vitamin D). The literature provides information on how vitamin D deficiency is associated with the presence of autoantibodies in patients with silicone breast implants [12]

The subject of adjuvants, as mentioned above, applies not only to implanted silicone implants, but also to substances contained in vaccines. The consequences that may arise from an abnormal immune reaction were noted in a 71-year-old male who observed progressive and severe bilateral rigidity of the shoulder and hip. Previously, for several years he was vaccinated with an influenza vaccine without complications. In the year of onset of symptoms, he received a quadrivalent influenza vaccine, recommended for older people. He described the occurrence of fevers and muscle pains which developed within a few hours after receiving the vaccine. He developed rigidity of the hip and shoulder joint with pain, which gradually deteriorated over the following days. The patient was examined in the emergency department 2 days later. At that time he felt the lack of constant stiffness and limiting the pain of the shoulder and hip girdle movements. The patient was diagnosed with polymyalgia rheumatic using the criteria of the American League of Rheumatism / American College of Rheumatology 2012 with morning stiffness lasting longer than 45 minutes, lack of rheumatoid factor, and hip pain [13]. Of the reported cases in the medical literature, 3 patients were tested for HLA types and found to be positive for HLA-DRB1 and HLA-DQB1, the same markers found in patients with this disease. It is therefore possible

that antigen exposure may act as a triggering factor in patients with a known predisposition to the disease [13].

Conclusions:

Autoimmune / auto-inflammatory disorders can be caused by silicone implants and vaccine adjuvants: they include the presence of autoantibodies, muscle and joint pain, lupus-like symptoms and hardened-like symptoms.

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