Immunologist's Little Dirty Secret Finger: A Case Report of Polyautoimmunity Following an Accidental Self-injection of Complete Freund's Adjuvant

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Adjuvants are substances that are able to potentiate the immune system reaction to a given antigen [1]. They are widely used in medicine, especially in vaccines, to induce a more potent response to a microbial antigen. This response would produce a higher titer of antibodies, which would eventually confer better protection. Adjuvants are also used in experimental models, mainly in animal models, to induce different diseases for research purposes [2]. The Freund's adjuvants are irreplaceable components of induction protocols of many experimental animal models of autoimmune disease [2]. The Freund's adjuvants include incomplete (IFA) and complete Freund's adjuvant (CFA). The latter has been used in the induction of several experimental models of autoimmune disease, such as experimental autoimmune encephalomyelitis (EAE), thyroiditis (EAT), and collagen induced arthritis (CIA) for many years.

We present a case of a patient who developed autoimmune/inflammatory syndrome induced by adjuvants (ASIA) syndrome following an accidental injection of CFA to his finger. We also discuss the link between CFA and autoimmunity.

PATIENT DESCRIPTION

In 1975, a 34-year-old male scientist, during his work in the laboratory, was accidentally injected with a small amount (0.15 ml) of CFA mixed with purified mouse collagen. A few days later his finger became swollen and he developed pleuritic chest pain accompanied by rigors and high fever. Several weeks later he was diagnosed with adjuvant disease that included arthritis, serositis, and epididymitis [3]. During the following years, he continued to present with episodes of arthritis and serositis. His laboratory examinations reported high erythrocyte sedimentation rate and C-reactive protein, and his immunologic laboratory tests were positive for anti-nuclear antibodies (ANA), anti-Ro (anti-SSA), and anti-La (anti-SSB). Anti-cardiolipin antibodies (IgM and IgG) and β-2-glycoprotein 1 (IgG) in a moderate titer and hyperproteinemia were detected. Furthermore, he was diagnosed with pulmonary embolism after he presented to the emergency department. A computed tomography angiography (CTA) was performed due to a sudden shortness of breath, and anticoagulation therapy was initiated. Due to the presence of anti-phospholipids antibodies he was diagnosed with antiphospholipid syndrome (APS). Moreover, he also developed dryness of the eyes and mouth and, based on this and his serological findings, a Sjögren's syndrome diagnosis was determined. From his clinical findings and laboratory results, and the positive history of exposure to a well-known adjuvant (CFA), the patient fulfilled the diagnostic criteria for ASIA syndrome.

In addition to the development of these autoimmune features, the patients experienced three episodes of Epstein–Barr virus (EBV) reactivation syndrome despite not being under immunosuppressive therapy. These episodes were described as characterized by extreme fatigue, sleep disturbances, depression, orthostatic hypotension, falls, and fainting. Each of these episodes lasted for 8 to 10 months and presented with a positive serology for viral capsid antigen (VCA) (IgG and IgM) and for Epstein–Barr nuclear antigen (EBNA) (IgG). Over the last years he also developed congestive heart failure following several coronary events, requiring several cardiac catheterizations and the implantation of cardiac resynchronization therapy (CRT) defibrillator (CRTD).

COMMENT

ASIA has been widely described in studies conducted thus far. The main feature of this syndrome is that all patients have a history

of being exposed to an adjuvant [1]. These adjuvants can be incorporated into vaccines, microbial agents, drugs, silicone implants, mineral oils, and other substances [2]. It is worth mentioning that the majority of people exposed to an adjuvant do not develop an autoimmune disease and there is a need for further factors, mainly genetic predisposition. The Freund's adjuvants are widely used in the field of autoimmunity due to their immunological characteristics and their ability to potentiate immune reactions against injected antigens and they are mainly used to induce inflammatory arthritis in animal models [4]. Although genetic screening was not performed in our case, we can reasonably assume that the patient was susceptible to developing autoimmunity as a little amount of CFA was sufficient to trigger various autoimmune diseases in this individual (i.e., APS, Sjögren's syndrome).

CFA are widely used in experimental mouse models as inducers of autoimmunity and are useful for understanding of the pathogenic mechanisms involved in human autoimmune diseases [4]. The classic model is the CIA in which injection of CFA mixed with purified mouse collagen is able to induce inflammatory arthritis, which explains the first manifestation in the reported patient. Indeed, a single intradermal injection of 0.1 ml of CFA in Sprague–Dawley rats at the base of the tail has been reported to be sufficient to induce arthritis [2]. Also, in MRL/ MpJ-lpr/lpr (MRL-lpr), which are a well-known model for autoimmunity, arthritis characterized by swelling and erythema of the hind legs was observed in 67–83% of mice treated with CFA [2].

EBV has been strongly linked to autoimmune diseases as it can cause a persistent latent infection with periodic reactivations, affecting B cells function and eliciting a strong T cell response. EBV has been suspected as an etiological factor in multiple autoimmune diseases, mainly multiple sclerosis (MS) and systemic lupus erythematosus (SLE).

ASIA syndrome is the best explanation for the complexity of our case. An international registry of ASIA syndrome was established in 2011 and by 2016 included 300 cases that fulfilled the criteria of ASIA syndrome. The registry showed that different types of adjuvants can induce the same autoimmune disease and the same adjuvant can induce different types of autoimmune disease. However, a more recent study, including 500 patients with ASIA syndrome, has shown that, within the reported immune diseases, 69% were well-defined immune diseases (autoimmune, autoinflammation, and mixed pattern diseases). Among the well-defined immune diseases following the exposure to adjuvants, polygenic autoimmune diseases were significantly higher than autoinflammatory disorders (92.7% vs. 5.8%, respectively, $P < 0.001$). Therefore, there is a common pathway between these adjuvants and autoimmune phenomena, which is best viewed as hyperstimulation of the immune system in those who are genetically prone to autoimmunity [5]. The latter consists of that an environmental trigger can induce chronic inflammation, leading to polyclonal activation of B cells, and in some cases, persistent activation of the adaptive immunity that eventually leads to the development of an autoimmune disease.

Although in our case there was only one injection of CFA, this amount can often be sufficient to trigger a chronic stimulation of the immune system that can explain the development of different types of autoimmune diseases in an individual after the exposure to one certain adjuvant. In addition, EBV is also known to chronically stimulate the immune system so perhaps there was a synergism between the two factors (the CFA adjuvant and reactivation of EBV virus) that led to the development of these different conditions over the years.

CONCLUSION

This is a case of a scientist, who following an accidental injection of CFA to his finger, describes the development of different autoimmune diseases, including inflammatory arthritis, serositis, Sjögren's syndrome, and APS. Physicians should be aware that the link between adjuvants exposure and autoimmunity is rare; however, it exists and in certain circumstances the consequences can be very severe, as in our case. Therefore, avoiding unnecessary exposure to adjuvants remains the most effective tool to prevent the development of potentially related autoimmune features.

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Discovery consists of looking at the same thing as everyone else does and thinking something different.

Albert Szent-Gyorgyi (1893–1986), Hungarian physiologist, credited with first isolating vitamin C and discovering the components and reactions of the citric acid cycle