

Systemic Lupus Erythematosus Induced by Autoimmune/ Inflammatory Syndrome Induced by Adjuvants. Is it Possible? Long-Term Follow-up and Literature Review

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There are reports in the literature describing a relationship between the use of adjuvants and development of autoimmune diseases.¹ In this article, we present a case of 37-year-old female patient who was hospitalized in 2010 due to severe, non-specific chest pain and purpura. Laboratory studies revealed thrombocytopenia 51×10^3 (normal values $140-440 \times 10^3$). Thrombotic thrombocytopenic purpura (TTP) with high titers of ADAMTS-13 antibody was diagnosed. TTP progression could not be halted despite treatment, necessitating administration of rituximab and removal of breast implants, what resulted in complete remission. Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) was diagnosed retrospectively.²

Moreover, immunological studies demonstrated presence of anti-nuclear antibodies (ANA) (anti-Sjögren's syndrome A [anti-SSA]) which returned to normal levels after rituximab and removal of implants, and remained normal during follow-up after two years.

In 2014, the patient reported to the Rheumatology Outpatient Clinic due to symptoms

of fatigue growing for over three months and mild pain in peripheral joints. Physical examination of the motor system revealed tenderness and edema of small joints in both hands. Laboratory studies demonstrated mild leukopenia $3.7 \times 10^3/\mu\text{L}$ (normal values $4-10 \times 10^3/\mu\text{L}$), reduced components of the complement system, and positive ANA (Table 1). Systemic lupus erythematosus (SLE) was diagnosed based on the Systemic Lupus International Collaborating Clinics criteria.³ Treatment with hydroxychloroquine (200 mg/day) was initiated with improvement. In 2016, the patient again experienced symptoms of fatigue; laboratory studies confirmed hypothyroidism and the presence of antithyroglobulin antibodies. Immunological studies showed increased ANA titer (anti-SSA, anti-nucleosome) as well as slightly reduced levels of C3 component of the complement system. Clinical improvement was obtained after supplementation of thyroid hormones. As determined retrospectively, the patient was six weeks pregnant at the time, but miscarried in the first trimester.

Adjuvants are substances capable of inducing severe immunological reaction.^{1,4} Silicone

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Table 1. Levels of individual immunological markers during observation

Time (year)	ANA titer	ENA specific nuclear antigens	C3	C4	ds-DNA
2010	1:320	SSA			
2012	1:100	-	1.0	0.3	-
2014	1:10,000	Ribosomal P SSA SM SM/RNP Nucleosome	0.50	0.08	-
2015		SSA Nucleosome	1.0	0.4	125
2016	1:1,000	SSA Nucleosome	0.8	0.3	68

ANA: Anti-nuclear antibodies; ENA: Extractable nuclear antigens (enzyme-linked immunosorbent assay), C3: C3 component of complement system; C4: C4 component of complement system; Ds-DNA: Anti-double stranded deoxyribonucleic acid antibody; SSA: Sjögren's syndrome A; SM: Smith antigen; RNP: Ribonucleoprotein; Normal values: C3 0.9-1.8 g/L, C4 0.1-0.4 g/L, anti-nuclear antibodies titer <1:160 (indirect immunofluorescence), double stranded deoxyribonucleic acid <100 IU/mL (enzyme-linked immunosorbent assay).

implants and other esthetic procedures are some of the best-examined adjuvants.⁵ It remains unelucidated why our patient developed high titers of antibodies and presented with clinical symptoms of SLE after two years of full remission of ASIA. It might be associated with the administration of rituximab. The patient had not suffered from infection or being under particular stress, which might be a provoking factor. Interestingly, in the subsequent years, we observed a decrease in her antibody titer or even complete clearance. We failed to find an explanation as to why the last blood tests showed reduced concentrations of one of the complement components, appearance of previously absent antithyroglobulin antibodies. We may only speculate that it might be related to early pregnancy and re-activation of mechanisms causing excessive stimulation of the immune system. To date, only isolated cases of ASIA associated with disturbances of thyroid function have been described in the literature.⁶

On the other hand, TTP may be present in 1-4% of patients with SLE and in most cases it is associated with elevated SLE activity.^{7,8} Presence of two antibodies, double stranded deoxyribonucleic acid and anti-SSA at the time of TTP diagnosis, is associated with the development of systemic connective tissue disease at later time.⁸

In conclusion, ASIA remains to be an enigmatic, poorly elucidated, and therefore, unpredictable disorder.

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