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ORIGINAL ARTICLE

The autoimmune/inflammatory syndrome induced by adjuvants (ASIA)/Shoenfeld's syndrome: descriptive analysis of 300 patients from the international ASIA syndrome registry

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Abstract The autoimmune/inflammatory syndrome induced by adjuvants (ASIA) is a recently identified condition in which the exposure to an adjuvant leads to an aberrant autoimmune response. We aimed to summarize the results obtained from the ASIA syndrome registry up to December 2016, in a descriptive analysis of 300 cases of ASIA syndrome, with a focus on the adjuvants, the clinical manifestations, and the relationship with other autoimmune diseases. A Web-based registry, based on a multicenter international study, collected clinical and laboratory data in a form of a questionnaire applied to patients with ASIA syndrome. Experts in the disease validated all cases independently. A comparison study regarding type of adjuvants and differences in clinical and laboratory findings was performed. Three hundred patients were analyzed. The mean age at disease onset was 37 years, and the mean duration of time latency between adjuvant stimuli and development of autoimmune conditions was 16.8 months, ranging between 3 days to 5 years. Arthralgia, myalgia, and chronic fatigue were the most frequently reported symptoms. Eighty-nine percent of patients were also diagnosed with another defined rheumatic/autoimmune condition. The most frequent autoimmune disease related to ASIA syndrome was undifferentiated connective tissue disease (UCTD). ASIA syndrome is associated with a high incidence of UCTD and positive anti-nuclear antibodies (ANA) test. Clinical and laboratory features differ from the type of adjuvant used. These findings may contribute to an increased awareness of ASIA syndrome and help physicians to identify patients at a greater risk of autoimmune diseases following the exposure to vaccines and other adjuvants. The ASIA syndrome registry provides a useful tool to systematize this rare condition.

Keywords Adjuvants · ANA · Autoantibodies · Autoimmune diseases · Chronic fatigue syndrome (CFS) · Fibromyalgia · Silicone · Systemic lupus erythematosus · Vaccines

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Introduction

The autoimmune/inflammatory syndrome induced by adjuvants (ASIA) was defined in 2011 by Shoenfeld et al. as a

condition in which the exposure to an adjuvant leads to an aberrant autoimmune response [1–4].

The authors unified under a common denominator autoimmune-based phenomenon induced by adjuvants. Four main conditions were identified as part of the ASIA syndrome: siliconosis, the Gulf War syndrome (GWS), the macrophagic myofasciitis syndrome (MMF), and post-vaccination phenomena. An adjuvant is defined as a substance that enhances antigen-specific immune response preferably without triggering one on its own. However, several studies in animal models and humans have shown the ability of adjuvants to trigger autoimmune phenomena [5–7].

Environmental factors have been shown to play a pivotal role in the pathogenesis of immune-mediated diseases [8]. Exposure to substances with an immune adjuvant activity, such as silicone, aluminum salts, and Freund's adjuvant contained in vaccines, and others, such as mineral oils, collagen, and hyaluronic acid used in cosmetic fillers and metal implants, has been associated with well-defined and non-defined immune-mediated diseases [9].

A genetic predisposition has also been implicated in the development of this condition [10] and seems a prerequisite which predisposes to the appearance of such autoimmune syndrome [11, 12].

Nonetheless, there is a debate on this condition, given the paucity of the reported cases, the difficulty to individuate a precise temporal-causal association, and the multitude of suspected adjuvants [13]. Thus, the main questions remain on the diversity of the clinical manifestations, the definition of such temporal association, and the clinically relevant adjuvant dose.

A possible tool to clarify the matter is to use a registry to collect relevant data on disease patterns. Registries are often the first approach into a new disease or area of inquiry [14]. For instance, the first report on the acquired immune deficiency syndrome was the case series report of pneumocystis pneumonia in Los Angeles [15]. Moreover, especially considering rare diseases, registries allow the gathering of enough data for epidemiological and/or clinical research studies. For instance, the analysis of the catastrophic antiphospholipid syndrome (CAPS) registry leads to the establishment of preliminary criteria for its classification and of guidelines for its management [16].

In this view, ASIA syndrome could be underreported because of unawareness and failure of attributing the syndrome to the exposure [17]. The ASIA syndrome registry was established in 2011 and aimed to collect data on the epidemiology, clinical and laboratory features of the ASIA syndrome. The registry consists of a multicentric, internationally published case reports and newly diagnosed cases of ASIA syndrome reported primarily by rheumatologists and other physicians. Data were collected in the form of a questionnaire, created for the purpose, and further analyzed by three experts on the subject (WA, QM, SY).

Herein, we aimed to summarize the results obtained from the ASIA syndrome registry up to December 2016, in a descriptive analysis of 300 cases of ASIA syndrome, with a focus on the adjuvants, the clinical manifestations, and the relationship with other autoimmune diseases.

Materials and methods

A questionnaire for ASIA cases was administered to physicians worldwide (Appendix). This was built to gather all the relevant aspects of ASIA syndrome according to the published preliminary criteria. The database was reviewed by physicians and rheumatologists for validation of the reported cases and to assure that patients fulfilled the propoed criteria for the ASIA syndrome. Patients were considered to have ASIA syndrome when two major criteria or one major criterion and two minor criteria were present (Table 1). We considered plausible only the exposure to the suspected adjuvant in the 10 years prior to disease manifestation.

Table 1 Proposed criteria for the diagnosis of "ASIA"

Major criteria
Exposure to an external stimulus (infection, vaccine, silicone, adjuvant) prior to clinical manifestations
The appearance of "typical" clinical manifestations
• 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
Minor criteria
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., multiple sclerosis, systemic sclerosis)

Three hundred forty-one patients were reported in the ASIA registry; 41 cases had to be excluded because they did not fulfill the inclusion criteria, missing data, or when the adjuvant was considered to have no biological plausibility or the exposure was reported to have occurred over 5 years from disease onset. Thus, the final cohort consisted of 300 cases.

Information on patient's medical history, including personal and familiar history of autoimmune diseases and allergies, was recorded. We then classified the cohort into three groups according to the suspected adjuvant suggested for each patient. The first group included 119 (39.7%) patients who received only vaccines, the second group included 103 (34.3%) patients who were exposed only to foreign materials—including silicone, metal implants, hyaluronic acid, and cosmetic fillers—and the third group consisted of 78 (26%) patients who were exposed to both vaccines and foreign materials.

Valuable information on time latency between adjuvant exposure and development of the first ASIA symptom, main clinical manifestations, antibody profile, and diagnosed autoimmune diseases was considered and compared between the three groups. Autoantibodies and other laboratory parameters were reported following the policy, techniques, and references provided from the centers from where the samples were collected.

Statistical analysis

SPSS version 20.0 (Chicago, IL, USA) was used. Normally distributed variables were summarized by using the mean and standard deviation (SD). Wilcoxon's matched pairs test and paired *t* test were performed. Univariate comparisons between nominal variables were calculated using chi-square (χ^2) test or Fisher's exact test where appropriate. Pearson's and Spearman's tests were used to perform the correlation analysis where appropriate. One-way ANOVA was used for multiple comparisons. Two-tailed *P* values were reported; *P* values less than 0.05 were considered significant.

Results

Patient demographic features

In the ASIA syndrome registry cohort, 86.7% ($N = 260$) of the patients were female and 13.3% ($N = 40$) were male. Mean age at diagnosis was 37.6 years, ranging from 4 to 82 years old. The mean latency period from time of implant until onset of clinical symptoms was 31 months (range 1 week–60 months).

Autoimmune susceptibility, defined as having personal or familiar history of autoimmune diseases, was documented in 20.3% of the cohort, of which 23 (7.7%) patients had a personal history and 40 (13.3%) had a familiar history of autoimmunity. Forty-seven (15.7%) patients had a history of allergy or an atopic profile. Of these patients, 25% had documented allergy to nickel and other metals.

Adjuvant foreign materials were identified in 105 patients prior to the development of ASIA syndrome. Cosmetic fillers were recognized as an adjuvant in 40 (38.8%) patients and consisted of mineral oil (Mo), hyaluronic acid (HA), polyalkylimide (PAL), polyacrylamide gel (PAC), and collagen. Metal implants were the suspected adjuvant in 45 (43.7%) patients and silicone breast implants in 18 patients (17.5%). Patients received various sorts of implants from different manufacturers. Concerning implants, all were silicone gel-filled breast implants. Local complications of cosmetic fillers were present in 15.4% of the patients and mainly consisted in inflammatory nodules, panniculitis, and cutaneous sarcoidosis.

Two-hundred thirty (76.7%) patients who developed ASIA syndrome received vaccines in the previous 10 years. Vaccines were the only identified adjuvant in 119 patients preceding the development of clinical manifestations. One hundred twenty-six patients (54.8%) received hepatitis B virus vaccine (HBVv), 48 (20.8%) received human papillomavirus vaccine (HPVv), 32 (13.9%) received influenza vaccine, and 24 received other vaccines (hepatitis A virus; diphtheria,

Table 2 Prevalence of relevant clinical findings in the ASIA registry cohort

Clinical findings	Frequency	Prevalence (%)
Arthralgia	184	61
Chronic fatigue	178	59
Myalgia	147	49
Sleep disturbances	112	37
Fever	101	34
General weakness	100	33
Arthritis	88	29
Neurological manifestations	78	26
Cognitive impairment	63	21
Sicca symptoms	55	18
Raynaud's phenomenon	48	16
Chronic rash	47	16
Lymphadenopathy	43	14
Photosensitivity	33	11
Mouth ulcers	18	6
Postural orthostatic tachycardia syndrome	13	4
Myositis	7	2

tetanus, and pertussis (DTP); and measles, mumps, and rubella (MMR)). The manufacturers of the different vaccines could not be identified.

Considering the HBVv, 16 patients developed the clinical manifestations after the first dose, 45 after the second dose, and 64 after the third dose. Considering the HPVv, 8 patients received only one dose, 17 received two doses, and 23 received three administrations. Early post-vaccination adverse events such as fever, rash, angioedema, flu-like symptoms, and serum sickness were reported by 5.9% of the patients.

Clinical findings

Various systemic and local manifestations were described and reported in our cohort (Table 2). The most common complaints reported by the patients were as follows: arthralgia, 61% (N = 184); chronic fatigue, 59% (N = 178); myalgia, 49% (N = 147); sleep disturbances, 37% (N = 112); general weakness, 33% (N = 100); and sicca symptoms, 18% (N = 55). Fever was present in 34% (N = 101) of the patients, arthritis in 29% (N = 88), and neurological manifestations in 26% (N = 78).

Autoimmune diseases

A clinically well-defined diagnosis was reported in 267 patients (89%), undifferentiated connective tissue disease (UCTD) being the most commonly reported disease in 26% (N = 78) of the patients, following fibromyalgia and/or chronic fatigue syndrome in 15.6%, SLE and other connective tissue diseases in 13%, and neurologic autoinflammatory diseases in 12%.

Sixteen (5.3%) patients had the diagnosis of vasculitis, mainly giant cell arteritis (GCA), two cases of ANCA-associated vasculitis, one case of Behçet's, one case of Henoch-Schonlein purpura, and one case of polyarteritis nodosa. Cutaneous sarcoidosis was diagnosed in two patients who were injected with poly-L-lactic acid (PAL) and hyaluronic acid methacrylate (HA), respectively. According to organ-specific autoimmune diseases, 12 patients had a diagnosis of type 1 diabetes mellitus (DM1), all of them related to HBV vaccine exposure except for one case, which was associated with the HPVv. Five patients were diagnosed with autoimmune liver diseases, all of them following HBVv.

In the HBV group, the most frequent diagnosis was UCTD (N = 24); in the HPV, fibromyalgia (N = 14); and in the influenza, UCTD (N = 15) or GCA (N = 8) (Table 3).

Laboratory findings

Anti-nuclear antibodies (ANA) were positive in 51.7% (N = 155) of the patients, 14 tested positive for anti-Sm and 12 for anti-dsDNA, 18 for anti-SSA and 5 patients had anti-SSB. Four patients were positive for antiphospholipid antibodies. Rheumatoid factor (RF) was found in 8% (N = 24), and only one patient tested positive for anti-CCP. Either anti-TPO or anti-RNP was detected in eight patients, and two patients with the diagnosis of systemic sclerosis were positive for anti-Scl70.

Treatment

Overall, 107 patients were treated with glucocorticoids, 57 with DMARDs, but data on the specific DMARD were not available for all the patients. Four patients underwent biological treatment, three with etanercept, and one with infliximab, all because of rheumatoid arthritis. Fifteen patients with SLE or vasculitis were treated with IVIg.

Statistics

Women had significantly more frequent fever (P = 0.007), arthralgia (P < 0.001), myalgia (P = 0.011), chronic pain (P = 0.002), cognitive impairment (P = 0.004), and general weakness (P < 0.001). Comparing the group who received vaccines to those who were exposed to foreign material, fever (P = 0.004), weight loss (P = 0.02), sleep disturbances (P = 0.034), headache (P = 0.006), and neurological involvement (P < 0.001) were more frequent in patients who received any vaccine, while cognitive impairment (P = 0.001) was more frequent in those patients exposed to foreign materials.

Concerning vaccines, myalgia was more frequent in those who received influenza vaccine (P < 0.05); arthritis in patients who received other vaccines than HBVv, HPVv, or influenza (P < 0.05); and neurological involvement in those who received HBVv (P < 0.05). Patients who were exposed to foreign materials were more frequently smokers (P < 0.001), and the most frequent symptom reported was arthralgia by 82 patients (79.6%).

Discussion

ASIA syndrome is a recently identified condition that relates the presence of an adjuvant to the occurrence of a protean clinical picture depicted by the proposed diagnostic criteria suggested by Shoenfeld et al. in 2011 [1]. Given the relative rarity of this condition and its recent identification, a registry has been created in order to increase the current knowledge on the clinical and laboratory presentation. ASIA syndrome has been so far described in several case reports, case series, and epidemiological studies and supported by animal models and in vitro experiments [6, 18–21]. The 300 cases gathered in the ASIA syndrome registry may help now

Table 3 Defined clinical diagnosis achieved in the ASIA registry cohort

Clinical diagnosis		Age	Gender	Vaccine adjuvant exposure	Foreign material adjuvant exposure
Vasculitis					
Giant cell arthritis/PMR	11	64–80 years, 72.3 ± 6.2	11 females, 1 male	Influenza vaccine	–
ANCA-associated vasculitis	2	53–54 years, 53.5 ± 0.7	2 females	HA (1), influenza vaccine (1)	–
Polyarteritis nodosa	1	32 years	Female	HBV vaccine	–
HS purpura	1	12 years	Female	HPV vaccine	–
Behçet's disease	1	18 years	Female	HPV vaccine	–
SLE and CTDs					
UCTD	78	15–82 years, 47.8 ± 15.8	71 females, 7 males	HBV vaccine (25), influenza vaccine (22), DTP vaccine (13), Td vaccine (12), smallpox vaccine (7), polio vaccine (5), DTP vaccine (3), HAV vaccine (3), HPV vaccine (3), pneumococcal vaccine (1), yellow fever vaccine (1), MMR vaccine (1), measles vaccine (1)	Metal implant (34), tooth amalgam (13), IUD (9), silicone (3), PAL and HA (1)
Systemic lupus erythematosus	18		16 females, 2 males	HBV vaccine (12), MMR vaccine (3), influenza vaccine (3), HPV vaccine (3), TD vaccine (2), DTP (1), DTD vaccine (1), HAV vaccine (1), oral typhoid vaccine (1), JE vaccine (1)	Mo (2), silicone (1)
Sjogren's syndrome	11	25–56 years, 39.9 ± 10.5	9 females, 2 males	HBV vaccine (6), HAV vaccine (1), oral typhoid vaccine (1), JE vaccine (1), MMR vaccine (1), influenza vaccine (1)	HA (3), PAC (2), PAL (1)
Rheumatoid arthritis	10	16–47 years, 29.7 ± 9.9	10 females	HBV vaccine (9), HPV vaccine (1)	–
Systemic sclerosis/morphea	5	31–55 years, 44.8 ± 11.4	5 females	HBV vaccine (2)	Silicone (2), PAC (1), metal implant (1), skin filler (1), IUD (1)
Juvenile rheumatoid arthritis	2	4–15 years, 9.5 ± 7.8	Female (1), male (1)	HBV vaccine (2)	–
Dermatomyositis	2	6 years	Female (1), male (1)	HBV vaccine (2)	–
Recurrent polychondrytis	1	39 years	Female	DTP vaccine	Silicone
APS	1	40 years	Female	HBV vaccine	–
MCTD	1	62 years	Female	HBV vaccine	–
Organ-specific					
Multiple sclerosis/optic neuritis/-neuromyelitis optica	20	15–55 years, 31.2 ± 8.9	18 females, 2 males	HBV vaccine (18), HPV vaccine (2)	–
Diabetes mellitus type 1	12	4–18 years, 11.0 ± 3.3	5 females, 7 males	HBV vaccine (10), HPV vaccine (2)	–
Guillain–Barré syndrome	8	11–66 years, 36.4 ± 24.2	6 females, 2 males	HBV vaccine (4), influenza vaccine (2), DTP vaccine (1), HAV vaccine (1), HPV vaccine (1)	–
Dysautonomic neuropathy	7	12–20 years, 15.3 ± 3.2	7 females	HPV vaccine (7)	–
POTS	6	12–22 years, 16.8 ± 3.8	6 females	HPV vaccine (6)	–
Autoimmune liver diseases	5	11–39 years, 26.5 ± 9.2	5 females	HBV (5), MMR vaccine (1), influenza vaccine (1)	–
Inflammatory bowel disease	6	11–23 years, 13.8 ± 5.2	4 females, 2 males	HBV vaccine (5), influenza vaccine (1)	–

Table 3 (continued)

Clinical diagnosis		Age	Gender	Vaccine adjuvant exposure	Foreign material adjuvant exposure
Interstitial lung disease	2	59–65 years, 62.0 ± 4.2	1 female, 1 male	–	PAL (1), metal implant (1)
Transverse myelitis	4	14–67 years, 33.0 ± 23.7	3 females, 1 male	HAV vaccine (1), HBV vaccine (3), HPV vaccine (1), DPT vaccine (1), MCV4 vaccine (1)	–
Autoimmune encephalitis	2	17–37 years, 27.0 ± 14.1	2 males	HBV vaccine (2)	–
Hemolytic anemia	1	14 years	Male	HBV vaccine	–
Autoimmune thyroiditis	1	14 years	Female	HPV vaccine	–
Adrenal insufficiency	1	9 years	Female	HBV vaccine	–
Inflammatory polyradiculopathy	1	53 years	Male	Influenza vaccine	–
Primary biliary cirrhosis	1	56 years	Female	–	PAC and HA
CIDP	1	52 years	Female	HBV vaccine	–
Others autoimmune/rheumatic diseases					
Fibromyalgia	36	11–66 years, 28.0 ± 14.2	34 females, 2 males	HPV vaccine (16), HBV vaccine (14), HAV vaccine (1), influenza vaccine (1)	Silicone (6)
Chronic fatigue syndrome	11	12–54 years, 29.7 ± 17.9	7 females, 4 males	HBV vaccine (8), HPV vaccine (2), intranasal influenza vaccine (1), DTd vaccine (1), HAV vaccine (1), JE vaccine (1), oral typhoid vaccine (1)	Silicone (1)
Sarcoidosis (2 skin)	3	50–53 years, 51.5 ± 2.1	Females(2)	HBV vaccine (1)	PLA (1), HAM (1)
Macrophagic myofasciitis	1	13 years	Female	HPV vaccine	–
Ankylosing spondylitis	1	35 years	Female	HAV vaccine	–
Adult Still's disease	1	27 years	Female	–	Silicone

Mo mineral oil, *HA* hyaluronic acid, *PAL* polyalkylimide gel, *PAC* polyacrylamide gel, *SLE* systemic lupus erythematosus, *CTD* connective tissue disease, *MCTD* mixed connective tissue disease, *UCTD* undifferentiated connective tissue disease, *CIDP* chronic inflammatory demyelinating polyneuropathy, *POTS* postural orthostatic tachycardia syndrome, *HAV* hepatitis A virus, *HBV* hepatitis B virus, *HPV* human papilloma virus, *DTP* diphtheria/tetanus/pertussis, *MMR* mumps/mumps/rubella, *MCV4* meningococcal conjugate vaccine 4, *JE* Japanese encephalitis, *IUD* intrauterine device

physicians to better recognize Shoenfeld's syndrome as a distinct entity.

The first evidence emerging from the registry is that an unequivocal diagnosis of a full-blown autoimmune disease is reached in the vast majority of patients with ASIA (89%), UCTD being the most frequent [22]. We excluded those cases in which (a) there was no literature reporting other case reports or case series linking the suspected adjuvants with the development of the full-blown autoimmune disease and (b) there was no biological plausibility, i.e., there was no literature on experimental models concerning the link between the suspected adjuvants with the development of the full-blown autoimmune disease. Moreover, we were more stringent in reducing the exposure time to the 10 years prior to the development of the symptoms. Even so, 11% of the cases could not be clinically defined, while patients experienced various non-specific clinical manifestations such as persistent fever, fatigue, headache, and cognitive impairment. The restriction of time exposure also caused the exclusion of several cases and was decided despite there is no mention on this issue in the ASIA proposed criteria. Nevertheless, this still remains a critical and controversial aspect of ASIA syndrome, since it is well known that the development of an autoimmune condition may even require up to 20 years even after the appearance of specific autoantibodies [23].

Concerning the clinical manifestations, some differences exist between patients exposed to foreign materials and those to vaccines, while intragroup differences could not be spotted out probably due to the small numbers in the subgroup analysis. Particularly, arthralgia was the most common manifestation in all groups, while patients who were suspected to develop post-vaccination autoimmune phenomena had a more frequent involvement in general symptoms such as fever and weight loss, sleep disturbances, and headache.

There were significant differences in clinical manifestations among men and women, probably due to the different adjuvant to which they were exposed. Neurologic manifestations were relatively common, ranging from multiple sclerosis to less specific symptoms including cognitive dysfunction and memory disturbances. Chronic pain and fatigue were also common and were often described in a fibromyalgia or in a chronic fatigue syndrome context.

Several intrinsic limitations of data gathered through spontaneous reporting systems are declaimed. All registry systems, even those owned by public health services for which reporting is mandated, suffer from underreporting [24]. It is likely that the ASIA registry is only representative of a small amount of cases given the novelty of the identification of the condition and the lack of knowledge on the condition by several physicians who were indeed the only ones allowed to send the data. This is further confirmed by the evidence that most of the data were obtained by rheumatologists. Nonetheless, case reports to the registry are not a random sample of cases found in the general population and therefore may have some bias. As any study where some information is collected retrospectively, the reports are rarely detailed. At best, the quality relies on the information recorded in clinical records, which is not always full or, on the other *scenario*, it relies on the memory of those who fill up the form. Since it is the clinician or researcher who self-select, the cases registered may be subjected to selection bias hampering its conclusion, because missing cases might have had very different outcomes [24]. Nonetheless, we provide data on a large cohort of patients diagnosed with ASIA syndrome. Several adjuvants may be linked with the development of ASIA syndrome, and a wide diversity in clinical manifestations and laboratory parameters has been observed. Given the limitations of the study, caution is needed in extrapolating conclusions from ASIA registry data to the general population. However, ASIA syndrome should be regarded as an exclusion diagnosis that must be considered whenever patients exposed to adjuvants develop general complaints suggesting an autoimmune process. The harmful role of adjuvants has already been recognized in the scientific community, and this is the case for instance of polyalkylimide whose use has been opposed for instance by the Dutch Society of Cosmetic Medicine [25]. There are data suggesting that silicone may be related to ASIA, and 200 cases were recently reported by Cohen-Tervaert et al. [18]. Concerning vaccines, their importance to the community should be once more stressed, the fundamental principle leading that vaccine must be administered following national laws and international guidelines and recommendations. Indeed, the rarity of the adverse manifestations strongly suggests that the benefits of the vaccines largely overwhelm the risks. The evidence of the occurrence of post-vaccination autoimmune phenomena, that needs to be fully clarified whether coincidental or causal, could be a stimulus to the development of safer and personalized vaccines.

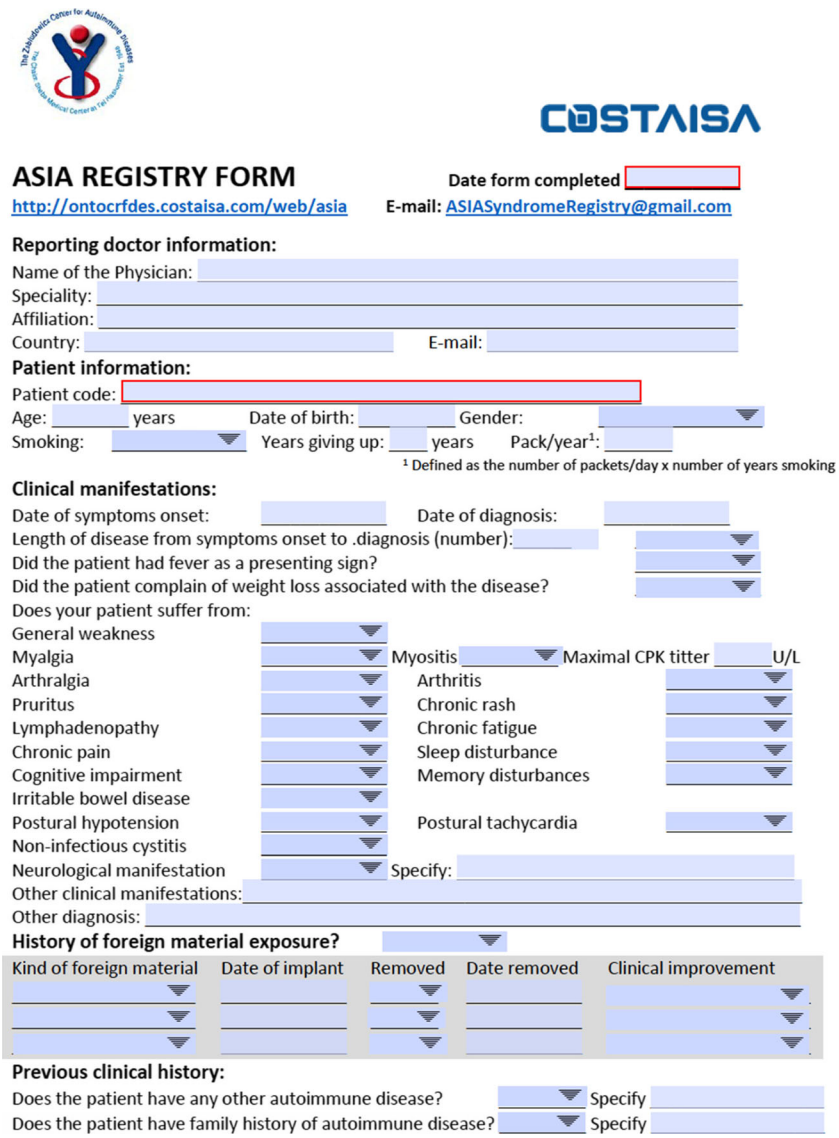
Physicians are encouraged to contribute to the ASIA registry and to the knowledge of this not-so-rare anymore condition in order to define the pathological mechanisms and to refine the clinical aspects.

Compliance with ethical standards

Conflict of interest YS appears in the Special vaccine compensation court in Washington US.

Appendix

1/3



COSTAISA

ASIA REGISTRY FORM Date form completed

http://ontocrfdes.costaisa.com/web/asia E-mail: ASIASyndromeRegistry@gmail.com

Reporting doctor information:

Name of the Physician:
Speciality:
Affiliation:
Country: E-mail:

Patient information:

Patient code:
Age: years Date of birth: Gender:
Smoking: Years giving up: years Pack/year[1]:

[1] Defined as the number of packets/day x number of years smoking

Clinical manifestations:

Date of symptoms onset: Date of diagnosis:
Length of disease from symptoms onset to .diagnosis (number):
Did the patient had fever as a presenting sign?
Did the patient complain of weight loss associated with the disease?
Does your patient suffer from:

General weakness			
Myalgia	Myositis	Maximal CPK titter	U/L
Arthralgia	Arthritis		
Pruritus	Chronic rash		
Lymphadenopathy	Chronic fatigue		
Chronic pain	Sleep disturbance		
Cognitive impairment	Memory disturbances		
Irritable bowel disease			
Postural hypotension	Postural tachycardia		
Non-infectious cystitis			
Neurological manifestation	Specify:		

Other clinical manifestations:
Other diagnosis:

History of foreign material exposure?

Kind of foreign material	Date of implant	Removed	Date removed	Clinical improvement

Previous clinical history:

Does the patient have any other autoimmune disease? Specify
Does the patient have family history of autoimmune disease? Specify

2/3

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Vaccination history in the past 10 years:

		First dose (date)	Second dose (date)	Third dose (date)
Hepatitis B Virus				
Human Papilloma Virus				
Hepatitis A Virus				
Influenza			How many times in the last 10 years?	
H1N1			How many times in the last 10 years?	
Pneumococcal		Last administration:		
Diphtheria-tetanus-pertussis		Last administration:		
Diphtheria-tetanus		Last administration:		
MMR		Last administration:		
BCG		Last administration:		
Yellow fever		Last administration:		
Typhus		Last administration:		
Other vaccines:		Date of administration:		

Does your patient have any allergic disease?

Allergic disease	Known allergen?	Allergen

Was any of the following serological test performed in the patient? :

ANA		dsDNA	
RF		RNP	
Scl70		Sm	
SS-A/Ro		SS-B/La	
Centromer		TPO	
CCP/ACPA		Low C4	
ASCA		Low C3	
Lupic anticoag.		Anticardiolipin	
Anti-B2GPI		Anti-TTG	
ANCA			
Other:			

Was a biopsy related to the ASIA syndrome performed?

Place biopsied	Date of biopsy	Acute inflammation	Chronic inflammation	Thrombosis	Granulomas

Was the MHC determined? MHC:

What was the treatment prescribed since the diagnosis?

Corticosteroids:		Dose: mg	
HCQ		Leflunomide	
Methotrexate		Tacrolimus	
Azathioprine		Cyclosporine	
Other immunosuppressed		Specify:	
Biologics		Specify:	
Other treatment		Specify:	

3/3

COSTAISA

What the patient followed?

Date: _____ Evolution: _____ Treatment: _____

Date: _____ Evolution: _____ Treatment: _____

Date: _____ Evolution: _____ Treatment: _____

Was the patient's case published? _____ If yes, please give us the reference.

Title: _____

Journal: _____ Number: ____ Vol.: _____ First page: _____

PMID: _____ DOI: _____

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