Autoimmune Disorders

Adjuvants and Other Risk Factors in Pathogenesis

Edited by
Abdulla Watad
Nicola Luigi Bragazzi
Yehuda Shoenfeld

WILEY

Autoimmune Disorders

Autoimmune Disorders

Adjuvants and Other Risk Factors in Pathogenesis

EDITED BY

Abdulla Watad

Rheumatology Unit and Zabludowicz Center for Autoimmune Diseases
Sheba Medical Center
Tel Aviv University
Tel-Hashomer
Israel

Nicola Luigi Bragazzi

Laboratory for Industrial and Applied Mathematics (LIAM)
Department of Mathematics and Statistics
York University
Toronto
Canada

Postgraduate School of Public Health
Department of Health Sciences (DISSAL)
University of Genoa
Genoa
Italy

Yehuda Shoenfeld

Reichman University
Herzliya
Israel

Zabludowicz Center for Autoimmune Diseases (Founder)
Sheba Medical Center
Tel-Hashomer
Israel

WILEY

This edition first published 2024

Registered Offices
John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, USA
John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester,
West Sussex, PO19 8SQ, UK

For details of our global editorial offices, customer services, and more information about Wiley products visit us at www.wiley.com.

Wiley also publishes its books in a variety of electronic formats and by print-on-demand. Some content that appears in standard print versions of this book may not be available in other formats.

Library of Congress Cataloging-in-Publication Data
Names: Watad, Abdulla, editor. | Bragazzi, Nicola Luigi, editor. | Shoenfeld, Yehuda, 1948- editor.
Title: Autoimmune disorders : adjuvants and other risk factors in pathogenesis / edited by Abdulla Watad, Nicola Luigi Bragazzi, Yehuda Shoenfeld.
Other titles: Autoimmune disorders (Watad)
Description: Hoboken, NJ : Wiley, 2024. | Includes bibliographical references and index.
Identifiers: LCCN 2024007509 (print) | LCCN 2024007510 (ebook) | ISBN 9781119858416 (hardback) | ISBN 9781119858423 (adobe pdf) | ISBN 9781119858447 (epub)
Subjects: MESH: Autoimmune Diseases—etiology | Autoimmune Diseases—physiopathology | Adjuvants, Immunologic—adverse effects
Classification: LCC RC600 (print) | LCC RC600 (ebook) | NLM QW 545 | DDC 616.97/8—dc23/eng/20240325
LC record available at https://lccn.loc.gov/2024007509
LC ebook record available at https://lccn.loc.gov/2024007510

Cover Design: Wiley
Cover Image: © Ruslan Batiuk /Adobe Stock Photos

Set in 8.75/11pt MeridienLTStd by Straive, Chennai, India

Contents

List of Contributors

Rojas-Villarraga Adriana
Research Institute
Fundación Universitaria de Ciencias de la Salud (FUCS)
Bogotá
Colombia

María Alejandra Martínez-Ceballos
Fundación Oftalmológica Nacional
Bogotá
Colombia

School of Medicine and Health Sciences
Universidad del Rosario
Bogotá
Colombia

Howard Amital
Zabludowicz Center for Autoimmune Diseases
Sheba Medical Center
Tel-Hashomer
Israel

Sackler Faculty of Medicine
Tel Aviv University
Tel Aviv
Israel

Department of Internal Medicine 'B'
Sheba Medical Center
Tel-Hashomer
Israel

Carina Benzvi
Zabludowicz Center for Autoimmune Diseases
Sheba Medical Center
Tel-Hashomer
Israel

Elena Bartoloni Bocci
Reumatologia
Dipartimento di Medicina e Chirurgia
Università di Perugia
Perugia
Italy

Vânia Borba
Internal Medicine Departmente
Rehaklik Dussnang AG
Dussnang
Thurgau
Switzerland

Nicola Luigi Bragazzi
Laboratory for Industrial and Applied Mathematics (LIAM)
Department of Mathematics and Statistics
York University
Toronto
Canada

Postgraduate School of Public Health
Department of Health Sciences (DISSAL)
University of Genoa
Genoa
Italy

Dana Butnaru
Department of Clinical Immunology
Hospital Clínico San Carlos
Complutense University of Madrid
Madrid
Spain

María P. Cruz-Domínguez
Internal Medicine Department
Unidad Médica de Alta Especiad
Hospital de Especialidades
"Dr. Antonio Fraga Mouret"
Centro Médico Nacional
"La Raza". Instituto Mexicano del Seguro Social
México City
México

Internal Medicine Department
División de Estudios de Posgrado
Facultad de Medicina
Universidad Nacional Autónoma de México
México City
México

Paula David
Department of Internal Medicine 'B'
Sheba Medical Center
Tel-Hashomer
Israel

Arad Dotan
Zabludowicz Center for Autoimmune Diseases
Sheba Medical Center
Tel-Hashomer
Israel

Sackler Faculty of Medicine
Tel Aviv University
Tel Aviv
Israel

Michael Ehrenfeld
Sackler Faculty of Medicine
Tel Aviv University
Tel Aviv
Israel

Zabludowicz Center for Autoimmune Diseases
Sheba Medical Center
Tel-Hashomer
Israel

Natalia Gavrilova
Federal State Budget Educational Institution of Higher Education "St. Petersburg State University"
University Emb.
7-9
Saint Petersburg
Russia

St Petersburg State University Hospital
Saint Petersburg
Russia

Roberto Gerli
Reumatologia
Dipartimento di Medicina e Chirurgia
Università di Perugia
Perugia
Italy

Montealegre Giovanni
Fundación Universitaria de Ciencias de la Salud (FUCS)
Hospital San José
Bogotá
Colombia

Gilad Halpert
Zabludowicz Center for Autoimmune Diseases
Sheba Medical Center
Tel-Hashomer
Israel

Department of Molecular Biology
Ariel University
Ariel
Israel

Abihai Lucas Hernández
Internal Medicine Department
Unidad Médica de Alta Especiad
Hospital de Especialidades
"Dr. Antonio Fraga Mouret"
Centro Médico Nacional
"La Raza". Instituto Mexicano del Seguro Social
México City
México

Hadas Hodadov
Sackler Faculty of Medicine
Tel Aviv University
Tel Aviv
Israel

Eitan Israeli
Zabludowicz Center for Autoimmune Diseases
Sheba Medical Center
Tel-Hashomer
Israel

Luis J. Jara
Research Division
Instituto Nacional de Rehabilitación
Mexico City
México

E. Kamaeva
Federal State Budget Educational Institution of Higher Education "St. Petersburg State University"
University Emb.
7-9
Saint Petersburg
Russia

Michael Kirby
Department of Molecular Biology and Adelson School of Medicine
Ariel University
Ariel
Israel

Igor Kudryavtsev
Almazov National Medical Research Centre
The Research Department
Saint Petersburg
Russia

Department of Immunology
Institution of Experimental Medicine
Petersburg State University
Saint Petersburg
Russia

Zora Lazurova
4th Department of Internal Medicine
Pavol Jozef Šafárik University
Kosice
Slovakia

Iana Leineman
Department of Therapy
Rheumatology
Examination of Temporary Disability and Quality of Medical Care Named After E.E. Eichwald
North-Western State Medical University
Named After I.I.Mechnikov
Saint Petersburg
Russia

Aaron Lerner
Zabludowicz Center for Autoimmune Diseases
Sheba Medical Center
Tel-Hashomer
Israel
Campus Ariel
Ariel University
Ariel
Israel

M. Lukashenko
Federal State Budget Educational Institution of Higher Education "St. Petersburg State University"
University Emb.
7-9
Saint Petersburg
Russia

Naim Mahroum
International School of Medicine
Istanbul Medipol University
Istanbul
Turkey

Anna Malkova
Laboratory of the Mosaic of Autoimmunity
St. Petersburg State University
Saint Petersburg
Russia

Gabriela Medina
Internal Medicine Department
Unidad Médica de Alta Especiad
Hospital de Especialidades
"Dr. Antonio Fraga Mouret"
Centro Médico Nacional
"La Raza". Instituto Mexicano del Seguro Social
México City
México

Internal Medicine Department
División de Estudios de Posgrado
Facultad de Medicina
Universidad Nacional Autónoma de México
México City
México

Alberto Ordinola-Navarro
Internal Medicine Department
Unidad Médica de Alta Especiad
Hospital de Especialidades
"Dr. Antonio Fraga Mouret"

Centro Médico Nacional
"La Raza". Instituto Mexicano del Seguro Social
México City
México

Internal Medicine Department
División de Estudios de Posgrado
Facultad de Medicina
Universidad Nacional Autónoma de México
México City
México

Mohammed Osman
Division of Rheumatology
Department of Medicine
University of Alberta
Edmonton
Alberta
Canada

Asher Pardo
Department of Occupational and Environmental Health
School of Public Health - Tel Aviv University and the Institute for Occupational Safety and Hygiene
Tel Aviv
Israel

Carlo Perricone
Reumatologia
Dipartimento di Medicina e Chirurgia
Università di Perugia
Perugia
Italy

Albert Pinhasov
Department of Molecular Biology and Adelson School of Medicine
Ariel University
Ariel
Israel

Gabriel M. Ramírez
Rheumatology Department
Hospital General de México
"Dr. Eduardo Liceaga"
México City
México

Uribe Rosa
Antioquia's Clinic
Itagüí
Colombia

Varvara Ryabkova
Laboratory of the Mosaic of Autoimmunity
Department of Pathology
Saint Petersburg State University
Saint Petersburg
Russia

Department of Hospital Therapy Named after Academician M.V. Chernorutskii
Research Institute of Rheumatology and Allergology
Pavlov First Saint Petersburg State Medical University
Saint Petersburg
Russia

Isa Seida
International School of Medicine
Istanbul Medipol University
Istanbul
Turkey

Kassem Sharif
Department of Gastroenterology
Sheba Medical Centre
Tel-Hashomer
Israel

Sackler Faculty of Medicine
Tel Aviv University
Tel Aviv
Israel

Zabludowicz Center for Autoimmune Diseases
Sheba Medical Center
Tel-Hashomer
Israel

Elena Shmerkin
Department of Molecular Biology and Adelson School of Medicine
Ariel University
Ariel
Israel

Yehuda Shoenfeld
Reichman University
Herzliya
Israel

Zabludowicz Center for Autoimmune Diseases
Sheba Medical Center
Tel-Hashomer
Israel

L. Soprun
Federal State Budget Educational Institution of Higher Education "St. Petersburg State University"
University Emb.
7-9
Saint Petersburg
Russia

St Petersburg State University Hospital
Saint Petersburg
Russia

Anna Starshinova
Almazov National Medical Research Centre
The Research Department
Saint Petersburg
Russia

Efrosiniia Talalai
Sackler Faculty of Medicine
Tel Aviv University
Tel Aviv
Israel

Zabludowicz Center for Autoimmune Diseases
Sheba Medical Center
Tel-Hashomer
Israel

Jan Willem Cohen Tervaert
Division of Rheumatology
Department of Medicine
University of Alberta
Edmonton
Alberta
Canada

Emeritus Professor of Medicine and Immunology
Maastricht University
Maastricht
The Netherlands

Milena Tocut
Department of Internal Medicine C
Wolfson Medical Center
Holon
Israel

Sackler Faculty of Medicine
Tel Aviv University
Tel Aviv
Israel

Olga Vera-Lastra
Internal Medicine Department
Unidad Médica de Alta Especiad
Hospital de Especialidades
"Dr. Antonio Fraga Mouret"
Centro Médico Nacional
"La Raza". Instituto Mexicano del Seguro Social
México City
México

Internal Medicine Department
División de Estudios de Posgrado
Facultad de Medicina
Universidad Nacional Autónoma de México
México City
México

Abdulla Watad
Rheumatology Unit and Zabludowicz Center for Autoimmune Diseases
Sheba Medical Center
Tel-Hashomer
Israel

Sackler Faculty of Medicine
Tel Aviv University
Tel Aviv
Israel

Section of Musculoskeletal Disease
Leeds Institute of Molecular Medicine
University of Leeds
Leeds
UK

Department of Internal Medicine 'B'
Sheba Medical Center
Tel-Hashomer
Israel

Institute of Oncology
Sheba Medical Center
Tel-Hashomer
Israel

Piotr Yablonskiy
Laboratory of the Mosaic of Autoimmunity
St. Petersburg State University
Saint Petersburg
Russia

St. Petersburg Research Institute of Phthisiopulmonology
Saint Petersburg
Russia

Gisele Zandman-Goddard
Department of Internal Medicine C
Wolfson Medical Center
Holon
Israel

Sackler Faculty of Medicine
Tel Aviv University
Tel Aviv
Israel

Yulia Zinchenko
St. Petersburg Research Institute of Phthisiopulmonology
Saint Petersburg
Russia

Introduction

"The Autoimmune/Inflammatory Syndrome Induced by Adjuvants (ASIA)" is a term introduced by one of the editors of this book, Prof. Yehuda Shoenfeld, to characterize a cluster of autoimmune and inflammatory disorders incited by exposure to various adjuvants [1]. These adjuvants can be encountered in diverse contexts, including vaccinations, silicone implants, and other materials, culminating in a spectrum of symptoms and medical conditions [2]. Given its relatively recent emergence in the medical landscape, with its introduction in 2011, ASIA remains a complex and evolving syndrome, with many facets yet to be fully elucidated. However, an accumulating body of evidence underscores the potential of specific adjuvants to incite autoimmune and inflammatory responses in susceptible individuals, often associated with HLA-DRB1 genetic factors [3]. Consequently, growing apprehension surrounds the safety of adjuvants integrated into certain vaccines and medical products. It is imperative to underscore that vaccines play a pivotal role in safeguarding public health. Over the years, they have played an instrumental role in eradicating lethal diseases such as smallpox, significantly reducing the prevalence of maladies such as measles and polio. Vaccines operate by invigorating the immune system to mount a defense against specific pathogens, all while sparing the individual from the disease itself. This herd immunity not only extends protection to vaccinated individuals but also shields the broader community, including those who cannot receive vaccines themselves. While vaccines can indeed elicit rare side effects, the immense benefits they confer decisively outweigh the associated risks, making them an indispensable tool in the preservation of public health. This book serves as a comprehensive exploration of ASIA and the diverse adjuvants capable of inciting autoimmune and inflammatory responses. We embark on a journey to decipher the substances implicated in ASIA syndrome, the array of symptoms and conditions it encompasses, and the current state of research in this realm. Our narrative commences by delving into the role of adjuvants in vaccines and the controversies regarding their safety. Though infrequent, some individuals exhibit heightened susceptibility to autoimmune and inflammatory reactions prompted by adjuvants in vaccines, culminating in an array of conditions including Guillain–Barré syndrome, multiple sclerosis, and lupus. We further scrutinize the involvement of silicone implants in the initiation of autoimmune and inflammatory responses. For years, silicone has been a cornerstone of breast implants [4], and though the safety of these implants has been subject to scrutiny [5], the connection between silicone and autoimmune maladies remains enigmatic. Nevertheless, a mounting body of evidence underscores that silicone exposure can incite autoimmune and inflammatory reactions, giving rise to conditions such as silicone implant syndrome, which can manifest with symptoms including fatigue, joint pain, and more. Beyond vaccines and silicone, we cast a spotlight on other adjuvants capable of inciting autoimmune and inflammatory reactions, encompassing commonly employed materials such as aluminum, prevalent in vaccines, and additional substances such as mesh and metals. We also conduct an exploration of autoimmune dysautonomia, a condition that has garnered substantial attention in recent years. Finally, we engage in a comprehensive discussion surrounding the diagnosis and treatment of ASIA as well as the prevailing controversies that encircle this syndrome. It is important to note that skepticism still pervades some medical circles regarding the existence of ASIA, with its symptoms and linkage to adjuvants often escaping recognition. Nonetheless, with an escalating awareness and an expanding body of research, the reality of ASIA as a genuine phenomenon affecting numerous individuals is becoming increasingly evident. In summation,

this book aspires to provide an exhaustive overview of ASIA and the manifold adjuvants capable of triggering autoimmune and inflammatory responses. Our hope is that this volume will raise awareness about this intricate syndrome and empower individuals to make informed decisions regarding their health and the medical products they encounter.

References

1. Shoenfeld, Y. and Agmon-Levin, N. (2011). 'ASIA' – autoimmune/inflammatory syndrome induced by adjuvants. *J. Autoimmun.* 36 (1): 4–8.
2. Seida, I., Alrais, M., Seida, R. et al. (2023). Autoimmune/inflammatory syndrome induced by adjuvants (ASIA): past, present, and future implications. *Clin. Exp. Immunol.* uxad033.
3. Arango, M.-T., Perricone, C., Kivity, S. et al. (2017). HLA-DRB1 the notorious gene in the mosaic of autoimmunity. *Immunol. Res.* 65 (1): 82–98.
4. Watad, A., Rosenberg, V., Tiosano, S. et al. (2018). Silicone breast implants and the risk of autoimmune/rheumatic disorders: a real-world analysis. *Int. J. Epidemiol.* 47 (6): 1846–1854.
5. Watad, A., Bragazzi, N.L., Amital, H., and Shoenfeld, Y. (2019). Hyperstimulation of Adaptive Immunity as the Common Pathway for Silicone Breast Implants, Autoimmunity, and Lymphoma of the Breast. *Isr. Med. Assoc. J.* 21 (8): 517–519.

1 Hyperstimulation of the Immune System

Hadas Hodadov[1] and Abdulla Watad[1,2,3,4,5]

[1]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[2]Department of Medicine 'B', Sheba Medical Center, Tel-Hashomer, Israel
[3]Rheumatology Unit and Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, Israel
[4]Section of Musculoskeletal Disease, Leeds Institute of Molecular Medicine, University of Leeds, Leeds, UK
[5]Institute of Oncology, Sheba Medical Center, Tel-Hashomer, Israel

Background

The immune system safeguards living organisms against constant assaults from both external and internal environments, detecting a wide variety of pathogens, cancer cells, and drugs (i.e., "non-self") and distinguishing them from the organism's own healthy tissue ("self") [1]. Two main subsections constitute the immune system: innate immunity, which provides immediate though incomplete protection against intruders and, at best, has only short-term memory; and adaptive immunity, offering a tailored response to each stimulus by learning to recognise previously encountered molecules [2]. Dysfunction of the immune system can lead to autoimmune diseases, autoinflammatory disorders, and cancer. Autoimmunity results from a complex interplay between genetic predisposition and environmental factors [3]. Adjuvants are molecules capable of triggering an immune response against specific or nonspecific antigens [4]. Biomaterials are routinely employed to address various conditions in nearly every medical specialty. However, certain substances within this category have been reported to possess adjuvanticity, thereby potentially accelerating or initiating autoimmune phenomena [5].

Biomaterials that are lined to hyperstimulation of the immune system (silicone, mesh and heavy metals)

Biomaterials play a pivotal role in addressing various healthcare issues, including tissue engineering, drug delivery, and medical implants. Their significance lies in the broad potential of these materials to offer support (i.e., scaffolds), allow modifications of chemical properties, and protect biologically active products (i.e., cells, proteins, and chemicals). Biomaterials encompass a diverse range of compounds with varying functions and structural features, ranging from naturally occurring biological macromolecules to fully synthetic coatings [6]. However, a noteworthy aspect,

Autoimmune Disorders: Adjuvants and Other Risk Factors in Pathogenesis, First Edition.
Edited by Abdulla Watad, Nicola Luigi Bragazzi, and Yehuda Shoenfeld.

though rare, is that certain biomaterials can chronically stimulate the immune system, resulting in excessive inflammation, fibrotic encapsulation, impaired healing, tissue destruction, or even rejection of medical devices [5]. The implantation of biomaterial elicits a host reaction that determines the integration outcome and the biological response of the implant. Upon implantation, the material interacts with the blood, causing protein adsorption to the biomaterial surface and the development of a temporary matrix that forms on and around the biomaterial. This matrix serves as the initial thrombus at the tissue-material interface. Protein adsorption and fibrin-predominant temporary matrix formation are closely linked in their mechanistic responses [7]. Injury to vascularized connective tissue initiates inflammatory responses by the innate immune system, leading to thrombus formation. The temporary matrix contributes components to foreign body reactions and wound healing. Cytokines, growth factors, mitogens, and other bioactive materials within the matrix create a rich environment of activating and inhibiting substances capable of modulating macrophage activity, along with the proliferation of other cell populations involved in inflammatory and wound-healing responses. Following the initial blood-material interactions and temporary matrix formation, both acute and chronic inflammation responses ensue [8].

Hyperstimulation syndrome induced by silicone breast implants

One significant biomaterial is silicone, a polymeric compound forming rubber-like materials used in various applications, including dental procedures, medical implants, and insulation. Silicone breast implants (SBIs), introduced in 1962, have been widely implanted in millions of individuals [9]. While there was an earlier perception that silicone is a biologically inert material, this notion has been refuted, with reported immunological effects induced by silicone. Silicone gel particles can migrate outside the outer shell post-rupture, and even migration through an intact shell has been demonstrated, known as "gel bleed" [10]. Silicon-containing particles captured by macrophages induce the release of IL-1, activate the NALP3 inflammasome and B cells, leading to an imbalance of regulatory T cells, responder T cells, and Th17 cells [11]. Animal studies have demonstrated that SBIs induce an adjuvant effect, increasing susceptibility to autoimmune/rheumatic disorders. The mechanisms by which SBIs induce autoimmune phenomena are numerous, involving dysregulation of both innate and adaptive immunity in individuals genetically predisposed to autoimmunity [9]. In recent years, inconsistent findings on the safety of SBIs have emerged. A large population-based study involving over 24,000 women with SBIs and approximately 100,000 age-matched controls revealed a significantly increased risk of autoimmune disease in women with SBIs, with an adjusted odds-ratio (OR) of 1.22 ([95% CI 1.18–1.26], $p < 0.001$). The risk was even higher (OR > 1.5, $p < 0.05$) in specific conditions such as sarcoidosis, systemic sclerosis, and Sjögren's syndrome [11]. Other studies have linked carrying SBIs with systemic clinical symptoms suggestive of rheumatic disorders, including fatigue, weakness, musculoskeletal pain, morning stiffness, and dry eyes and mouth [12]. Plausible mechanisms explaining the link between SBIs and autoimmune phenomena have been proposed, as supported by animal model studies. For example, injecting silicone gel in NZB mice induced proteinuria and autoimmune hemolytic anemia [13], while implanting silicone gel or silicone oil in MRL lpr/lpr mice increased anti-Ds-DNA antibodies [14]. In a rat model study, five genes (Fes, Aif1, Gata3, Tlr6, and Tlr2) were identified as hub genes likely linked to the immune responses induced by silicone. Four of these genes (Aif1, Gata3, Tlr6, and Tlr2) have been associated with autoimmunity as target genes or disease markers [15]. Thus, SBIs may trigger immune responses, with various immune reactions detected after silicone implantation.

Hyperstimulation syndrome induced by mesh

Mesh, a loosely woven sheet, constitutes another crucial biomaterial, with the commonly used polypropylene (PP) mesh being a strong yet flexible synthetic implant. PP, the second most widely

manufactured type of plastic globally, finds application in various products such as furniture, electronic components, and medical devices [16]. Utilized since the 1960s for hernia repair surgeries and since the 1990s for urinary incontinence and pelvic organ prolapse, PP implants have enhanced surgical outcomes and reduced recurrence risks. Initially considered an inert plastic, chemically inactive to minimize patient complications, a contrasting notion has emerged, suggesting mesh-related complications, particularly the body's immunological reaction to the implanted material [17]. Some researchers propose that PP mesh may induce a systemic autoimmune inflammatory disorder, akin to women with SBIs induced by adjuvants. PP implants elicit a rapid and effective acute inflammatory response followed by a chronic body reaction. Local inflammatory reactions after mesh insertion may lead to systemic upregulation of inflammatory mediators, primarily regulated by monocytes and macrophages at the implant tissue interface. These cells, known to produce various cytokines, particularly IL-6, play a crucial role in the acute phase of the inflammatory process, regulating local and systemic responses [18]. One theory explaining the chronic foreign body response to mesh involves oxidative processes, with oxidation causing PP degradation, resulting in chronic inflammation and a subsequent systemic autoimmune inflammatory disorder. Supporting evidence for mesh acting as an adjuvant includes the appearance of systemic autoimmune symptoms shortly after mesh placement and the remission of symptoms after mesh removal [19]. A recent study evaluated patients with implanted PP for the development of systemic illness. Thirty-nine out of 40 patients presented with chronic fatigue, and 38 of 40 patients had myalgia, both occurring shortly after surgery. All patients fulfilled the diagnostic criteria for ASIA syndrome. In 45% of patients, there was a diagnosis of a well-established autoimmune disease, suggesting that PP mesh implants increase the risk of developing autoimmune diseases by acting as an adjuvant [20].

Hyperstimulation syndrome induced by metals

Metals and metal alloys, combinations of metal elements, have been widely utilized as medical implants for over a century across various medical specialties. They find application in a diverse range of medical devices, from solid metal implants in orthopedics to bioelectronics such as pacemakers or neurostimulators [21]. These metal implants are chosen as biomedical materials due to their numerous advantages over other materials, including high mechanical strength, good electrical conductivity, durability, and excellent biological compatibility. Ideally, metal implants should not cause any undesired reactions; however, interactions between the implant and the surrounding tissue can lead to complications, including infection, inflammation, and foreign body response. While heavy metals and their salts have previously been demonstrated to play a role in causing allergic diseases, recent evidence suggests their key involvement in the induction or exacerbation of autoimmune diseases [22]. The mechanism by which heavy metals trigger autoimmunity is not fully understood, but its comprehension is not necessary for establishing an association between them. Manifestations of autoimmunity may include the production of autoantibodies, an increase in serum IgG and IgE, polyclonal activation of B and T lymphocytes, infiltration of destructive inflammatory cells into different target organs, and the deposition of immune complexes in vascular sites [22]. Another suggested mechanism is that metal compounds may exert toxic effects on the immune system, leading to the malfunctioning of the system as a whole. Despite an incomplete understanding of the mechanism, there is a growing notion supported by extensive research that the interaction of metals with the immune system may lead to immunodysregulation, resulting in autoimmune diseases [23].

Link among foreign bodies, chronic stimulation, and lymphoproliferative disorders

Following acute inflammation, chronic inflammation at the implant site is characterized by the presence of mononuclear cells, including monocytes and lymphocytes. An implant may continue

to elicit a chronic inflammatory response lasting for months or longer, marked by a broader immune cell infiltration, encompassing both myeloid and lymphoid cells. After the resolution of acute and chronic inflammatory responses, granulation tissue, identified by the presence of macrophages, infiltration of fibroblasts, and neovascularization, is observed in the new healing tissue [5]. It is hypothesized that any breast implant, whether saline or silicone, may release silicone corpuscles over time. Factors such as trauma causing microfractures, exposure to temperature or pressure, ultraviolet radiation, oxidation, and chemical reactions can accelerate this process. When the permeability of the elastomer is impaired, the physiological seroma in the space between the elastomer surface and the fibrous capsule reacts and transports the resulting polydimethylsiloxane compound from the implant surface, encountering the fibrous capsule [24]. The fibrous capsule acts as a physiological protective barrier against products from the intracapsular environment. If met with silicone particles, regardless of the mechanism, an immune response may be generated, potentially leading to a silicone-induced granuloma. If the fibrous capsule ruptures and exposes its contents to the extracapsular space, the immune reaction can trigger a systemic immune response [24]. Some patients may develop an autoimmune reaction to silicone components. A common finding related to silicone implant complications is a silicone-induced granuloma of the breast implant capsule (SIGBIC). Histologically, SIGBIC is formed by extracellular and/or intracellular silicone, numerous histiocytes, chronic granulomatous inflammatory infiltrate with multinucleated giant cells, and an infiltrate of mixed lymphocytes – T and B without atypia [25]. Another rare but serious complication is anaplastic large cell lymphoma (ALCL), a subtype of non-Hodgkin lymphoma of T cells [26]. An association between ALCL and saline and silicone implants exists. The first case of ALCL associated with breast implants was published in 1997 [27], and by 2011, the Food and Drug Administration published a statement confirming 60 cases of ALCL associated with prostheses. ALCL affects the fibrous capsule around the implant, rarely appears as a solid mass, and does not involve the breast parenchyma. As in SIGBIC, the mechanism of ALCL may involve an immune response induced by the silicone material in the implant, leading to an immune overreaction and monoclonal neoplasia with activated T lymphocytes. Additionally, in saline or silicone implants, the capsules may be responsible for chronic local inflammation with T-cell activation and clonal expansion [28]. Furthermore, in case of capsular disruption, silicone-containing particles are transported to the regional lymph nodes, causing a marked adjuvant effect. Silica particles induce a type-2 inflammatory response characterized by an increase in IgE and IgG1 and chronic activation of T cells [25]. The pathophysiology of ALCL and SIGBIC is very similar, with the only difference being the monoclonal neoplasia induced by the activation of T lymphocytes in ALCL, prompting consideration of whether ALCL is an evolution of SIGBIC. Clinically, ALCL may present as fluid filling within the intracapsular space (seroma), while SIGBIC is most often present as an intracapsular mass. Both conditions usually have an excellent prognosis once the fibrous capsule is excised and the implant is removed [28].

Studies on silicone, metals, and the risk of lymphoma

Due to evidence on breast implant-associated ALCL, some reports propose a possible development of ALCL in relation to other implants, such as metal. Examples include ALCL associated with a stainless-steel fixation plate for tibial fracture repair or after the placement of dental implants [29, 30]. Chronic inflammation and antigenic stimulation caused by the presence of implants (such as silicone, metal, or others) are suggested as possible neoplastic triggers. Resembling lymphomas associated with other inflammatory conditions, implant-associated lymphomas are believed to share similar features, including development after prolonged inflammation, localization to a confined body space, and a latency period until the development of lymphoid malignancy. This can be attributed to ongoing inflammation and chronic stimulation of adaptive immune cells with polyclonal activation, which may result in monoclonality and ultimately lead to the development

of lymphoma in genetically susceptible hosts [21]. The relationship between SBIs and lymphoma can be demonstrated by the well-established link between Epstein–Barr virus (EBV) infection and the risk of lymphoma. The pathogenesis of EBV-associated lymphomas involves dysregulation between inflammatory and inflammation-neutralizing processes, leading to the production of radical oxygen species that can cause the impairment of critical oncogenic pathways, such as p53, promoting lymphomagenesis and eventually lymphomas [31]. As mentioned, silicone particles are capable of infiltrating lymph nodes, not only local but also distal ones, and enhancing antigen-specific immune reactions. Thus, the presence of SBIs is comparable to latent infection, with EBV leading to chronic nonspecific stimulation of adaptive immunity, polyclonal activation, monoclonal activation, and eventually, the development of lymphoma.

References

1. Nicholson, L.B. (2016). The immune system. *Essays Biochem.* 60 (3): 275–301.
2. Yatim, K.M. and Lakkis, F.G. (2015). A brief journey through the immune system. *Clin. J. Am. Soc. Nephrol.* 10 (7): 1274–1281.
3. Brodin, P. and Davis, M.M. (2017). Human immune system variation. *Nat. Rev. Immunol.* 17 (1): 21–29.
4. Watad, A., Sharif, K., and Shoenfeld, Y. (2017). The ASIA syndrome: basic concepts. *Mediterr. J. Rheumatol.* 28 (2): 64–69.
5. Anderson, J.M., Rodriguez, A., and Chang, D.T. (2008). Foreign body reaction to biomaterials. *Semin. Immunol.* 20 (2): 86–100.
6. Mariani, E., Lisignoli, G., Borzì, R.M., and Pulsatelli, L. (2019). Biomaterials: foreign bodies or tuners for the immune response? *Int. J. Mol. Sci.* 20 (3): 636.
7. Veiseh, O. and Vegas, A.J. (2019). Domesticating the foreign body response: recent advances and applications. *Adv. Drug Deliv. Rev.* 144: 148–161.
8. Higgins, D.M., Basaraba, R.J., Hohnbaum, A.C. et al. (2009). Localized immunosuppressive environment in the foreign body response to implanted biomaterials. *Am. J. Pathol.* 175 (1): 161–170.
9. Hajdu, S.D., Agmon-Levin, N., and Shoenfeld, Y. (2011). Silicone and autoimmunity: silicone and autoimmunity. *Eur. J. Clin. Investig.* 41 (2): 203–211.
10. Maijers, M.C., de Blok, C.J.M., Niessen, F.B. et al. (2013). Women with silicone breast implants and unexplained systemic symptoms: a descriptive cohort study. *Neth. J. Med.* 71 (10): 534–540.
11. Watad, A., Rosenberg, V., Tiosano, S. et al. (2018). Silicone breast implants and the risk of autoimmune/rheumatic disorders: a real-world analysis. *Int. J. Epidemiol.* 47 (6): 1846–1854.
12. Balk, E.M., Earley, A., Avendano, E.A., and Raman, G. (2016). Long-term health outcomes in women with silicone gel breast implants: a systematic review. *Ann. Intern. Med.* 164 (3): 164.
13. McDonald, A.H., Schneider, M., Gudenkauf, L. et al. (1998). Silicone gel enhances the development of autoimmune disease in New Zealand black mice but fails to induce it in BALB/cAnPt mice. *Clin. Immunol. Immunopathol.* 87 (3): 248–255.
14. Schaefer, C.J. and Wooley, P.H. (1999). The influence of silicone implantation on murine lupus in MRL lpr/lpr mice. *J. Rheumatol.* 26 (10): 2215–2221.
15. Huang, X., Zhou, Y., Liu, W. et al. (2017). Identification of hub genes related to silicone-induced immune response in rats. *Oncotarget* 8 (59): 99772–99783.
16. Kowalik, C.R., Zwolsman, S.E., Malekzadeh, A. et al. (2022). Are polypropylene mesh implants associated with systemic autoimmune inflammatory syndromes? A systematic review. *Hernia* 26 (2): 401–410. 12 [cited 2022 Mar 2]. https://link.springer.com/10.1007/s10029-021-02553-y.
17. Dias, E.R.M., Pivetta, L.G.A., de Carvalho, J.P.V. et al. (2021). Autoimmune [auto-inflammatory] syndrome induced by adjuvants (ASIA): case report after inguinal hernia repair with mesh. *Int. J. Surg. Case Rep.* 84: 106060.
18. Di Vita, G., Patti, R., Sparacello, M. et al. (2008). Impact of different texture of polypropylene mesh on the inflammatory response. *Int. J. Immunopathol. Pharmacol.* 21 (1): 207–214.
19. Chughtai, B., Sedrakyan, A., Mao, J. et al. (2017). Is vaginal mesh a stimulus of autoimmune disease? *Am. J. Obstet. Gynecol.* 216 (5): 495.e1–495.e7.

20. Tervaert, J.W.C. (2018). Autoinflammatory/autoimmunity syndrome induced by adjuvants (Shoenfeld's syndrome) in patients after a polypropylene mesh implantation. *Best Pract. Res. Clin. Rheumatol.* 32 (4): 511–520.
21. U.S Food & Drug Administration (FDA) (2019). Biological responses to metal implants.
22. Mishra, K.P. (2020). Heavy metals exposure and risk of autoimmune diseases: a review. *Arch. Immunol. Allergy* 3 (2): 22–26.
23. Pollard, K.M. (2015). Environment, Autoantibodies, and Autoimmunity. *Front. Immunol.* 6: 60. 11 [cited 2022 Mar 2];6. http://journal.frontiersin.org/Article/10.3389/fimmu.2015.00060/abstract.
24. de Faria Castro Fleury, E., D'Alessandro, G.S., and Lordelo Wludarski, S.C. (2018). Silicone-induced granuloma of breast implant capsule (SIGBIC): histopathology and radiological correlation. *J Immunol Res* 2018: 1, 9.
25. de Fleury, E.F.C. (2020). Synchronous breast implant associated anaplastic large cell lymphoma (BIA-ALCL) and silicone induced granuloma of breast implant capsule (SIGBIC): What to learn. *Radiol. Case Rep.* 15 (10): 1736–1742.
26. Kim, B., Predmore, Z.S., Mattke, S. et al. (2015). Breast implant–associated anaplastic large cell lymphoma: updated results from a structured expert consultation process. *Plast. Reconstr. Surg. Glob. Open* 3 (1): e296.
27. Keech, J.A. and Creech, B.J. (1997). Anaplastic T-cell lymphoma in proximity to a saline-filled breast implant. *Plast. Reconstr. Surg.* 100 (2): 554–555.
28. de Fleury, E.F.C., Rêgo, M.M., Ramalho, L.C. et al. (2017). Silicone-induced granuloma of breast implant capsule (SIGBIC): similarities and differences with anaplastic large cell lymphoma (ALCL) and their differential diagnosis. *Breast Cancer (Dove Med. Press)* 9: 133–140.
29. Palraj, B., Paturi, A., Stone, R.G. et al. (2010). Soft tissue anaplastic large T-cell lymphoma associated with a metallic orthopedic implant: case report and review of the current literature. *J. Foot and Ankle Surg.* 49 (6): 561–564.
30. Yoon, H.-J., Choe, J.-Y., and Jeon, Y.K. (2015). Mucosal CD30-positive T-cell lymphoproliferative disorder arising in the oral cavity following dental implants: report of the first case. *Int. J. Surg. Pathol.* 23 (8): 656–661.
31. Bizjak, M., Selmi, C., Praprotnik, S. et al. (2015). Silicone implants and lymphoma: the role of inflammation. *J. Autoimmun.* 65: 64–73.

2

Autoimmune/Inflammatory Syndrome Induced by Adjuvants (ASIA): Genetics, Immunization, and Autoimmunity

Carlo Perricone, Elena Bartoloni Bocci, and Roberto Gerli

Reumatologia, Dipartimento di Medicina e Chirurgia, Università di Perugia, Perugia, Italy

Introduction

Shoenfeld and Agmon-Levin in 2011 coined the term "ASIA – Autoimmune/inflammatory Syndrome Induced by Adjuvants" [1] to describe several clinical conditions, namely siliconosis, Gulf War Syndrome (GWSy), Macrophage Myofasciitis (MMF) syndrome, sick building syndrome (SBS), and postvaccination phenomena, which share similar signs or symptoms [2] and that have as a common denominator the presence of an adjuvant that triggers a disreactivity of the immune system.

Clustering of autoimmune diseases (AID) in families is well recognized, supporting a common genetic background [3]. Environmental factors (infectious agents, dust, vaccines, etc.) or other agents acting as adjuvants (dust, silicone, aluminum salts, etc.) cooperate on a genetically prone individual triggering autoimmune phenomena [4–9]. Enhanced immunogenicity might lead to reactogenicity in a process that does not always begin involving pathological stimulation [10]. Interestingly, several autoimmune conditions, such as Sjögren's syndrome [11], undifferentiated connective tissue disease [12], and silicone implant incompatibility syndrome [13], share pathogenetic aspects with ASIA syndrome. The mechanisms that have been proposed as instrumental in ASIA are different (Table 2.1).

Genetic background

The presence of a favoring genetic background as a prerequisite for the development of such conditions may explain their rarity [14]. Notably, loci in the human leukocyte antigen (HLA),

Autoimmune Disorders: Adjuvants and Other Risk Factors in Pathogenesis, First Edition.
Edited by Abdulla Watad, Nicola Luigi Bragazzi, and Yehuda Shoenfeld.

Table 2.1 Mechanism of adjuvant-induced autoimmunity.

Mechanisms of adjuvants-induced autoimmunity
• Alteration of the host's immune system
• Polyclonal activation of B cells
• Activation of autoreactive T cells
• Effects on immune regulatory cells
• Effects on virus-induced antibodies
• Molecular mimicry
• Bystander activation
• Epitope spreading
• Anti-idiotypic network
• Changing the host's antigens
• Expression of HLA family antigens
• Modification of surface antigens
• Induction of novel antigens
• Interaction with TLRs
• Antigens translocation
• Release of inflammatory cytokines

HLA, Human leukocyte antigen; TLRs, Toll-like receptors.

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]. An in silico study has shown that six genes (TGFB1, interferon-γ, CD4, FCGR3A, FCGR2A, and HLA-DRB1) and 33 pathways seem to be common to Guillain–Barré Syndrome (GBS), Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), and Idiopathic (or immune) Thrombocytopenic Purpura (ITP) [15]. Not surprisingly, all these genes are well-known participants to the immune response: for instance, CD4 and interferon-γ implicate the response mediated by Th1 lymphocytes, TGFB1 suggests a role for T-regulatory cells, the two IgG FC receptors suggest an antibody-mediated immunopathology or immunomodulation, and finally, HLA-DRB1 suggests antigen processing for presentation to T cells [15].

GWSy has been associated with two genetic polymorphic sites of the enzyme paraxonase, involved in the hydrolysis of organophosphate pesticides and nerve gases, influencing their toxicity to mammals and man [16, 17], while MMS has been associated with the HLA class II allele DRB1*01 [18]. Indeed, HLA-DRB1*01 allele was highly represented in people with MMS who had received in the previous decade immunization against hepatitis B or A viruses or tetanus toxoid, all containing aluminum hydroxide as adjuvant. Kappel et al. evaluated three sisters carrying the BRCA-1 gene mutation who had a preventive mastectomy and were reconstructed with silicone breast implants. In all sisters within a period of four years, symptoms suggesting ASIA were observed, suggesting a possible common genetic background [19].

Young et al. reported that silicone breast-implanted women with autoimmune symptoms were more frequently displaying HLA-DR5 and HLA-DQ2 when compared to asymptomatic women with silicone implants [20]. This raises the possibility that HLA genotype might serve as a marker for women who are predisposed to develop autoimmune symptoms following exposure to silicone gel breast implants.

Postvaccination phenomena are more likely to occur in patients with genetic predisposition. A recent study suggested that giant cell arteritis/polymyalgia rheumatica can represent a very rare event developing postinfluenza vaccination, especially in persons at higher spontaneous risk such as those carrying DRB1*13:01 haplotype [21]. Narcolepsy is a chronic disabling neurologic

disorder characterized by severe irresistible daytime sleepiness and abnormal sleep–wake patterns [22]. The disorder is uncommon in children younger than five years. However, in 2010, an increased incidence of narcolepsy was observed in Finland and Sweden in children and adolescents immunized with the H1N1 ASO3-adjuvanted pandemic influenza vaccine. The European Medicines Agency confirmed the existence of this association, which has since been detected in England, Ireland, France, and Norway [23]. In these cases, narcolepsy appeared associated with HLA DQB1*0602, which is more common in Northern countries than elsewhere [24].

Post-SARS-CoV-2 vaccination autoimmune phenomena are extremely rare, strengthening the safety of the vaccines. Following vaccination, the most commonly reported diseases associated with new-onset events were immune thrombocytopenia, Guillain–Barré syndrome, and myocarditis. Immune thrombocytopenia, psoriasis, IgA nephropathy, and SLE, on the other hand, were the most reported illnesses associated with relapsing episodes. Both occurrences were widely linked to the mRNA-1273 SARS-CoV-2 vaccine, which was followed by Sinovac-CoronaVac and ChAdOx1 nCoV-19 vaccine (AZD1222). Germano et al. described cases of Guillain–Barrè syndrome following SARS-CoV-2 vaccination [25] usually presenting as an acute inflammatory demyelinating polyradiculoneuropathy and occurring after the first vaccine dose. Ramdas et al. reported seven cases of new-onset myasthenia gravis in timely association with SARS-CoV-2 vaccination, including a pediatric case [26]. Şendur et al. [27] suggested that the frequencies of HLA-B*35 and HLA-C*04 alleles could be higher in SARS-CoV-2 vaccine-induced subacute thyroiditis compared with controls [HLA-B*35: 13 (93%) versus 40 (40%), $p<0.001$; HLA-C*04: 13 (93%) versus 43 (43%), $p<0.001$, respectively]. Moreover, more severe thyrotoxicosis was seen in patients having HLA-B*35 and HLA-C*04 homozygous alleles [free thyroxine: 4.47 ng/dL (3.77–5.18) versus 1.41 ng/dL (1.22–2.63), $p = 0.048$]. Interestingly, already in 2011, an association among influenza vaccine, HLA-B*35, and subacute thyroiditis was suggested [28].

Thus, vaccination effects may clearly differ substantially due to the genetic background of the recipient individual, and the vaccination schedule would be better if personalized [29]. Thomas et al. have revised this issue gathering a number of examples of genotype/gene polymorphisms mainly in the HLA gene family, related to interindividual variation to vaccination [30]. The advances in the fields of immunology, genetics, molecular biology, bioinformatics, and the Human Genome Project have allowed for the emergence of the field of vaccinomics that encompasses the fields of immunogenetics and immunogenomics as applied to understanding the mechanisms of heterogeneity in immune responses to vaccines [31].

Hence, it is imperative to pursue the aim of implementing the tools of genomics and proteomics to allow the prediction of those population sets more likely to be nonresponsive or develop adverse reactions to vaccines.

Immunity

The trigger of a dysregulated immune response is different according to the agent serving as "adjuvant." Noteworthy, those vaccines that are associated with postvaccination phenomena are usually targeted toward an infectious agent that is per se capable of triggering that specific phenomenon. This suggests similar immunopathogenic mechanisms between vaccines and infectious agents as triggering factors of autoimmune diseases (ADs). Usually, the phenomena occur much more frequently following the infection than following vaccination [32]. For instance, this is the case of the recently described myocarditis following anti-SARS-CoV-2 vaccines that occurs at a much lower frequency than in patients affected by COVID-19 [33]. At the same extent, Guillain–Barré occurs at a greater frequency after influenza virus infection than it does after vaccination [34].

The anti-idiotype immune response can explain the common increased prevalence of certain reactions to vaccines and the infectious agent. Indeed, a specific antigen can trigger the production of second particular antibodies against the first ones [35]. Surprisingly, these second antibodies may be capable of binding to receptors that the initial antigen may attach to. This is significant

since many autoimmune or -inflammatory reactions elicited by COVID-19 vaccinations have previously been reported with vaccines, whose principal immunopathogenic mechanism is the anti-idiotype immune response [36, 37].

Another possible mechanism by which an altered immune response may occur is due to molecular mimicry. This refers to the concept that an immune response, initially directed at bacterial or viral antigens, can target host molecules that share sequence homology or structural similarities with microbial epitopes [38]. Adjuvants accomplish this task by mimicking specific sets of evolutionarily conserved molecules (liposomes, lipopolysaccharides (LPSs), unmethylated CpG dinucleotide-containing DNA, etc.). On the other hand, the adjuvant may induce autoimmunity through the polyclonal activation of B cells [39], through an enhanced cytokine production and the expansion of autoreactive T cells [40].

For instance, SARS-CoV-2 might trigger AIDs [41] through molecular mimicry [42, 43]. Moreover, the history of past infections can alter the reactogenicity of mRNA vaccines through a cross-reactivity mechanism [44]. A greater reactogenicity may confer higher protection but could generate more adverse events. It is relevant to underline that patients with AIDs are not at increased risk of adverse events associated with vaccination [45], possibly due to the effect of immunomodulatory drugs on vaccine immunogenicity.

Concerning the case of narcolepsy, it is possible that molecular mimicry involving cross-reactivity of H1N1-specific T cells and hypocretin-producing neurons is the key pathogenic mechanism. Cross-reactive $CD4^+$ T cells that recognize both a foreign H1N1 epitope and an epitope present on hypocretin-producing cells and presented by HLA-DQB1*06:02 by antigen presenting cells could, however, be involved with a major overall alteration of T-cell subsets [46].

Other mechanisms that may be involved in postvaccination phenomena include neutrophil activation facilitated by NETosis and platelet activation especially in vaccine-induced immune thrombotic thrombocytopenia (VITT) [47]. VITT has also been related to the activation of the NF-kB pathway in which plasminogen activator inhibitor-1 (PAI-1) plays a relevant role in thrombotic events. The NF-kB may exert a direct effect on monocytes, leading to the production of cytokines, such as interleukin 1β, that in turn generate a procoagulant state [48, 49].

Autoimmunity

A full-blown autoimmune disease has been occasionally described following exposure to adjuvants, and several autoimmune conditions including Sjögren's syndrome and undifferentiated connective tissue disease seem to share pathogenetic aspects with ASIA syndrome. Despite debated [50], pollution dust seems to be capable of eliciting an autoimmune response in people experiencing the terroristic attack at the World Trade Center in New York on 11 September 2001 [51–53]. The debris and dust were composed of an amalgam of glass fibers, silica, asbestos, polycyclic aromatic hydrocarbons, dioxin, furans, and polychlorinated biphenyls, and the firefighters and the policemen who worked at the site of the attack later developed autoimmune diseases at an increased incidence than general population.

VITT is a thrombotic thrombocytopenia developing in a very small proportion of patients after exposure to ChAdOx1 and Ad26.COV.2 vaccines anti-SARS-CoV-2 [54]. In these patients, mostly females <50 years old, the presence of platelet-activating antibodies directed against platelet factor 4 (PF4) has been documented, suggesting a similarity to Heparin-associated thrombocytopenia, which is characterized by the presence of antibodies against the heparin/(PF4) complex, generating thrombocytopenia and thrombosis due to platelet activation. Indeed, the binding of PF4 with endothelial cells and platelets facilitates platelet aggregation and thrombus formation [55]. PF4 can interact with the double-stranded DNA of the vaccine vector, and the PF4/DNA vector complex recognized by the antigen-presenting cells allows in some patients the production of antibodies against PF4 [56].

SARS-CoV-2 infection and vaccines have represented an interesting model for the possible development of autoimmunity. In this context, García-Bravo et al. [57] have shown that myositis-related autoantibodies were more frequent during the pandemic, in particular anti-MDA5. In contrast, in 2021, after the vaccination campaigns, the most common antibodies were anti-PL7 and/or anti-PL12.

Other evidence of increased reactogenicity in patients with chronic inflammatory diseases vaccinated with anti-SARS-CoV-2 vaccines have been aroused. These patients may report more myalgia and fatigue after exposure to vaccines [58].

A recent study suggested that SARS-CoV-2 vaccines may trigger neurological autoimmunity including central nervous system demyelinating diseases, inflammatory peripheral neuropathies, myositis, myasthenia, limbic encephalitis, and giant cell arteritis, usually with a favorable outcome and good tolerance to revaccinations [59].

Conclusion

The panorama that we are now facing has dramatically changed. Vaccines save millions of lives each year, improving the quality of life, and this has proved even more true in these times of COVID-19 pandemic. If we consider the billions of doses of anti-SARS-CoV-2 vaccines administered, these can be considered extremely safe, as well as all the vaccines that are recommended in the general population. The novel vaccines technology, including the mRNA-based vaccinations, has significantly contributed to this generational leap in terms of vaccines safety, even in patients already suffering from an autoimmune disease [60].

Still, in the view of personalized medicine, a better knowledge of the relationships among a specific vaccine, the genetic background, and the immune milieu would even allow to avoid the occurrence of any autoimmune-rheumatic adverse events. At the same extent, although silicone implants are safe for the vast majority of subjects, screening for preexisting autoimmune phenomena and genetic testing appear useful tools for risk stratification before the implantation in predisposed subjects to dodge autoimmune phenomena and subsequent explanation surgeries [61].

References

1. Shoenfeld, Y. and Agmon-Levin, N. (2011). ASIA–autoimmune/inflammatory syndrome induced by adjuvants. *J. Autoimmun.* 36: 4–8.
2. Perricone, C., Colafrancesco, S., Mazor, R.D. et al. (2013). Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) 2013: unveiling the pathogenic, clinical and diagnostic aspects. *J. Autoimmun.* 47: 1–16. https://doi.org/10.1016/j.jaut.2013.10.004.
3. Arango, M.T., Perricone, C., Kivity, S. et al. (2017). HLA-DRB1 the notorious gene in the mosaic of autoimmunity. *Immunol. Res.* 65 (1): 82–98. https://doi.org/10.1007/s12026-016-8817-7.
4. Carvalho, J.F., Barros, S.M., Branci, J.C., and Fonseca, J.E. (2011). ASIA or Shoenfeld's syndrome: highlighting different perspective for diffuse chronic pain. *Acta Rheumatol Port* 36: 10–12.
5. Meroni, P.L. (2011). Autoimmune or auto-inflammatory syndrome induced by adjuvants (ASIA): old truths and a new syndrome? *J. Autoimmun.* 36: 1–3.
6. Shoenfeld, Y., Huges, G.R.V., and Agmon-Levin, N. (2012). The spectrum of ASIA: 'autoimmune (autoinflammatory) syndrome induced by adjuvants'. *Lupus* 21: 118–120.
7. Rosenblum, H., Shoenfeld, Y., and Amital, H. (2011). The common immunogenic etiology of chronic fatigue syndrome: from infections to vaccines via adjuvants to the ASIA syndrome. *Infect. Dis. Clin. N. Am.* 25: 851–863.
8. Israeli, E., Agmon-Levin, N., Blank, M., and Shoenfeld, Y. (2009). Adjuvants and autoimmunity. *Lupus* 18: 1217–1225.

9. Molina, V. and Shoenfeld, Y. (2005). Infection, vaccines and other environmental triggers of autoimmunity. *Autoimmunity* 38: 235–245. https://doi.org/10.1080/08916930500050277.
10. Watad, A., Quaresma, M., Brown, S. et al. (2017). Autoimmune/inflammatory syndrome induced by adjuvants (Shoenfeld's syndrome) – an update. *Lupus* 26: 675–681. https://doi.org/10.1177/0961203316686406.
11. Colafrancesco, S., Perricone, C., Priori, R. et al. (2014). Sjögren's syndrome: another facet of the autoimmune/inflammatory syndrome induced by adjuvants (ASIA). *J. Autoimmun.* 51: 10–16. https://doi.org/10.1016/j.jaut.2014.03.003.
12. Scanzi, F., Andreoli, L., Martinelli, M. et al. (2017). Are the autoimmune/inflammatory syndrome induced by adjuvants (ASIA) and the undifferentiated connective tissue disease (UCTD) related to each other? A case-control study of environmental exposures. *Immunol. Res.* 65 (1): 150–156. https://doi.org/10.1007/s12026-017-8912-4.
13. Cohen Tervaert, J.W. (2018). Autoinflammatory/autoimmunity syndrome induced by adjuvants (ASIA; Shoenfeld's syndrome): a new flame. *Autoimmun. Rev.* 17 (12): 1259–1264. https://doi.org/10.1016/j.autrev.2018.07.003.
14. Borba, V., Malkova, A., Basantsova, N. et al. (2020). Classical examples of the concept of the ASIA syndrome. *Biomolecules* 10 (10): 1436.
15. McGarvey, P.B., Suzek, B.E., Baraniuk, J.N. et al. (2014). In silico analysis of autoimmune diseases and genetic relationships to vaccination against infectious diseases. *BMC Immunol.* 15: 61. https://doi.org/10.1186/s12865-014-0061-0.
16. Haley, R.W., Billecke, S., and La Du, B.N. (1999). Association of low PON1 type Q (type A) arylesterase activity with neurologic symptom complexes in Gulf War veterans. *Toxicol. Appl. Pharmacol.* 157 (3): 227–233. https://doi.org/10.1006/taap.1999.8703.
17. Mackness, B., Durrington, P.N., and Mackness, M.I. (2000). Low paraoxonase in Persian Gulf War Veterans self-reporting Gulf war syndrome. *Biochem. Biophys. Res. Commun.* 276 (2): 729–733. https://doi.org/10.1006/bbrc.2000.3526.
18. Guis, S., Pellissier, J.F., Nicoli, F. et al. (2002). HLA-DRB1*01 and macrophagic myofasciitis. *Arthritis Rheum.* 46 (9): 2535–2537. https://doi.org/10.1002/art.10465.
19. Kappel, R.M., Cohen Tervaert, J.W., and Pruijn, G.J. (2014). Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) due to silicone implant incompatibility syndrome in three sisters. *Clin. Exp. Rheumatol.* 32 (2): 256–258.
20. Young, V.L., Nemecek, J.R., Schwartz, B.D. et al. (1995). HLA typing in women with breast implants. *Plast. Reconstr. Surg.* 96 (7): 1497–1519.
21. Liozon, E., Parreau, S., Filloux, M. et al. (2021). Giant cell arteritis or polymyalgia rheumatica after influenza vaccination: a study of 12 patients and a literature review. *Autoimmun. Rev.* 20 (2): 102732. https://doi.org/10.1016/j.autrev.2020.102732.
22. Buonocore, S.M. and van der Most, R.G. (2022). Narcolepsy and H1N1 influenza immunology a decade later: what have we learned? *Front. Immunol.* 13: 902840. https://doi.org/10.3389/fimmu.2022.902840.
23. Juvodden, H.T., Viken, M.K., Nordstrand, S.E.H. et al. (2020). HLA and sleep parameter associations in post-H1N1 narcolepsy type 1 patients and first-degree relatives. *Sleep* 43 (3): zsz239. https://doi.org/10.1093/sleep/zsz239.
24. Viste, R., Lie, B.A., Viken, M.K. et al. (2021). Narcolepsy type 1 patients have lower levels of effector memory CD4$^+$ T cells compared to their siblings when controlling for H1N1-(Pandemrix™)-vaccination and HLA DQB1*06:02 status. *Sleep Med.* 85: 271–279. https://doi.org/10.1016/j.sleep.2021.07.024.
25. Germano F, Bellucci M, Grisanti S, Beronio A, Grazzini M, Coco E, Tassinari T, Della Cava F, De Michelis C, Baldi O, Sivori G, Murialdo A, Cabona C, Durando P, Uccelli A, Schenone A, Franciotta D, Benedetti L. COVID-19 vaccine-related Guillain-Barré syndrome in the Liguria region of Italy: a multicenter case series. *J. Neurol. Sci.* 2022;440:120330. https://doi.org/10.1016/j.jns.2022.120330).
26. Ramdas, S., Hum, R.M., Price, A. et al. (2022). SARS-CoV-2 vaccination and new-onset myasthenia gravis: a report of 7 cases and review of the literature. *Neuromuscul. Disord.* 32 (10): 785–789.
27. Şendur, S.N., Özmen, F., Oğuz, S.H. et al. (2022). Association of human leukocyte antigen genotypes with severe acute respiratory syndrome coronavirus 2 vaccine-induced subacute thyroiditis. *Thyroid* 32 (6): 640–647. https://doi.org/10.1089/thy.2022.0010.

28. Hernán Martinez, J., Corder, E., Uzcategui, M. et al. (2011). Subacute thyroiditis and dyserythropoesis after influenza vaccination suggesting immune dysregulation. *Bol. Asoc. Med. P. R.* 103 (2): 48–52.
29. Nanishi, E., Dowling, D.J., and Levy, O. (2020). Toward precision adjuvants: optimizing science and safety. *Curr. Opin. Pediatr.* 32 (1): 125–138. https://doi.org/10.1097/MOP.0000000000000868.
30. Thomas, C. and Moridani, M. (2010). Interindividual variations in the efficacy and toxicity of vaccines. *Toxicology* 278 (2): 204–210. https://doi.org/10.1016/j.tox.2009.10.008.
31. Poland, G.A., Ovsyannikova, I.G., Jacobson, R.M., and Smith, D.I. (2007). Heterogeneity in vaccine immune response: the role of immunogenetics and the emerging field of vaccinomics. *Clin. Pharmacol. Ther.* 82 (6): 653–664. https://doi.org/10.1038/sj.clpt.6100415.
32. Nahra, V., Makandura, M., Anthony, D.D., and Mattar, M. (2022). A case series on the COVID-19 vaccines and possible immune-related adverse events: a new challenge for the rheumatologists. *Cureus* 14 (9): e29660. https://doi.org/10.7759/cureus.29660.
33. Heidecker, B., Dagan, N., Balicer, R. et al. (2022). Myocarditis following COVID-19 vaccine: incidence, presentation, diagnosis, pathophysiology, therapy, and outcomes put into perspective. A clinical consensus document supported by the Heart Failure Association of the European Society of Cardiology (ESC) and the ESC Working Group on Myocardial and Pericardial Diseases. *Eur. J. Heart Fail.* 24 (11): 2000–2018. https://doi.org/10.1002/ejhf.2669.
34. Salmon, D.A., Proschan, M., Forshee, R. et al. (2013). Association between Guillain-Barré syndrome and influenza A (H1N1) 2009 monovalent inactivated vaccines in the USA: a meta-analysis. *Lancet* 381 (9876): 1461–1468. https://doi.org/10.1016/S0140-6736(12)62189-8.
35. Murphy, W.J. and Longo, D.L. (2022). A possible role for anti-idiotype antibodies in SARS-CoV-2 infection and vaccination. *N. Engl. J. Med.* 386 (4): 394–396. https://doi.org/10.1056/NEJMcibr2113694.
36. Shukla, A.K. and Misra, S. (2022). Clinical implications of anti-idiotype antibodies in COVID-19. *J. Basic Clin. Physiol. Pharmacol.* https://doi.org/10.1515/jbcpp-2022-0123.
37. Bellucci, M., Germano, F., Grisanti, S. et al. (2022). Case report: post-COVID-19 vaccine recurrence of Guillain-Barré syndrome following an antecedent parainfectious COVID-19-related GBS. *Front. Immunol.* 13: 894872. https://doi.org/10.3389/fimmu.2022.894872.
38. Segal, Y. and Shoenfeld, Y. (2018). Vaccine-induced autoimmunity: the role of molecular mimicry and immune crossreaction. *Cell. Mol. Immunol.* 15 (6): 586–594. https://doi.org/10.1038/cmi.2017.151.
39. Tovey, M.G., Lallemand, C., Meritet, J.F., and Maury, C. (2006). Adjuvant activity of interferon alpha: mechanism(s) of action. *Vaccine* 24 (Suppl 2): S2-46-7. https://doi.org/10.1016/j.vaccine.2005.01.117.
40. van Aalst, S., Ludwig, I.S., van der Zee, R. et al. (2017). Bystander activation of irrelevant $CD4^+$ T cells following antigen-specific vaccination occurs in the presence and absence of adjuvant. *PLoS One* 12 (5): e0177365. https://doi.org/10.1371/journal.pone.0177365.
41. Rodríguez, Y., Rojas, M., Beltrán, S. et al. (2022). Autoimmune and autoinflammatory conditions after COVID-19 vaccination. New case reports and updated literature review. *J. Autoimmun.* 132: 102898. https://doi.org/10.1016/j.jaut.2022.102898.
42. Liu, Y., Sawalha, A.H., and Lu, Q. (2021). COVID-19 and autoimmune diseases. *Curr. Opin. Rheumatol.* 33: 155–162. https://doi.org/10.1097/BOR.0000000000000776.
43. Anaya, J.-M., Herrán, M., Beltrán, S., and Rojas, M. (2022). Is post-COVID syndrome an autoimmune disease? *Expet Rev. Clin. Immunol.* https://doi.org/10.1080/1744666X.2022.2085561. [
44. Vizcarra, P., Haemmerle, J., Velasco, H. et al. (2021). BNT162b2 mRNA COVID-19 vaccine Reactogenicity: the key role of immunity. *Vaccine* 39: 7367–7374. https://doi.org/10.1016/j.vaccine.2021.10.074.
45. Wieske, L., Kummer, L.Y.L., van Dam, K.P.J. et al. (2022). Risk factors associated with short-term adverse events after SARS-CoV-2 vaccination in patients with immune-mediated inflammatory diseases. *BMC Med.* 20: 100. https://doi.org/10.1186/s12916-022-02310-7.
46. Singh, A.K., Mahlios, J., and Mignot, E. (2013). Genetic association, seasonal infections and autoimmune basis of narcolepsy. *J. Autoimmun.* 43: 26–31. https://doi.org/10.1016/j.jaut.2013.02.003.
47. Holm, S., Kared, H., Michelsen, A.E. et al. (2021). Immune complexes, innate immunity, and NETosis in ChAdOx1 vaccine-induced thrombocytopenia. *Eur. Heart J.* 42: 4064–4072. https://doi.org/10.1093/eurheartj/ehab506.
48. Mattsson, E., Herwald, H., and Egesten, A. (2003). Superantigens from *Staphylococcus aureus* induce procoagulant activity and monocyte tissue factor expression in whole blood and mononuclear cells via IL-1 beta. *J. Thromb. Haemost.* 1: 2569–2576. https://doi.org/10.1111/j.1538-7836.2003.00498.x.

49. Iba, T., Umemura, Y., Wada, H., and Levy, J.H. (2021). Roles of coagulation abnormalities and microthrombosis in sepsis: pathophysiology, diagnosis, and treatment. *Arch. Med. Res.* 52: 788–797. https://doi.org/10.1016/j.arcmed.2021.07.003.
50. Sacks, H.S., Smirnoff, M., Carson, D. et al. (2022). Autoimmune conditions in the World Trade Center general responder cohort: a nested case-control and standardized incidence ratio analysis. *Am. J. Ind. Med.* 65 (2): 117–131. https://doi.org/10.1002/ajim.23313.
51. Webber, M.P., Moir, W., Zeig-Owens, R. et al. (2015). Nested case-control study of selected systemic autoimmune diseases in World Trade Center rescue/recovery workers. *Arthritis Rheumatol.* 67 (5): 1369–1376. https://doi.org/10.1002/art.39059.
52. Miller-Archie, S.A., Izmirly, P.M., Berman, J.R. et al. (2020). Systemic autoimmune disease among adults exposed to the September 11, 2001 terrorist attack. *Arthritis Rheumatol.* 72 (5): 849–859. https://doi.org/10.1002/art.41175.
53. Brite, J., Miller-Archie, S.A., and Cone, J. (2022). The relationship between 9/11 exposure, systemic autoimmune disease, and post-traumatic stress disorder: a mediational analysis. *Int. J. Environ. Res. Public Health* 19 (11): 6514. https://doi.org/10.3390/ijerph19116514.
54. Lavin, M., Elder, P.T., O'Keeffe, D. et al. (2021). Vaccine-induced immune thrombotic thrombocytopenia (VITT) – a novel clinico-pathological entity with heterogeneous clinical presentations. *Br. J. Haematol.* 195: 76–84. https://doi.org/10.1111/bjh.17613.
55. Cai, Z., Greene, M.I., Zhu, Z., and Zhang, H. (2020). Features structural, functions P.F.4. That occur in heparin-induced thrombocytopenia (HIT) complicated by COVID-19. *Antibodies* 9: 52. https://doi.org/10.3390/antib9040052.
56. McGonagle, D., De Marco, G., and Bridgewood, C. (2021). Mechanisms of immunothrombosis in vaccine-induced thrombotic thrombocytopenia (VITT) compared to natural SARS-CoV-2 infection. *J. Autoimmun.* 121: 102662. https://doi.org/10.1016/j.jaut.2021.102662.
57. García-Bravo, L., Calle-Rubio, M., Fernández-Arquero, M. et al. (2022). Association of anti-SARS-COV-2 vaccine with increased incidence of myositis-related anti-RNA-synthetases auto-antibodies. *J. Transl. Autoimmun.* 5: 100160. https://doi.org/10.1016/j.jtauto.2022.100160.
58. Yang, M.M., Taylor, K.E., Paez, D. et al. (2022). Reactogenicity of the messenger RNA SARS-CoV-2 vaccines associated with immunogenicity in patients with autoimmune and inflammatory disease. *Arthritis Care Res.* 74: 1953–1960. https://doi.org/10.1002/acr.24894.
59. Doubrovinskaia, S., Mooshage, C.M., Seliger, C. et al. (2022). Neurological autoimmune diseases following vaccinations against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): a follow-up study. *Eur. J. Neurol.* https://doi.org/10.1111/ene.15602.
60. Assawasaksakul, T., Lertussavavivat, T., Sathitratanacheewin, S. et al. (2022). Comparison of immunogenicity and safety of inactivated, adenovirus-vectored, and heterologous adenovirus-vectored/mRNA vaccines in patients with systemic lupus erythematosus and rheumatoid arthritis: a prospective cohort study. *Vaccines (Basel).* 10 (6): 853. https://doi.org/10.3390/vaccines10060853.
61. Ribeiro, P.D.C. and Sato, E.I. (2022). Autoimmune/autoinflammatory syndrome induced by adjuvants: a focus on silicone. *Clin. Rheumatol.* 41 (11): 3275–3283. https://doi.org/10.1007/s10067-022-06274-0.