

Symptoms of ASIA Syndrome in a Female Patient with Tattoos – A Case Report

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Abstract: The autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA) is a relatively novel clinical entity characterized by the emergence of autoimmune-like manifestations triggered by exposure to substances with immunostimulatory potential in genetically predisposed individuals. Such substances, called adjuvants, encompass infectious and toxic agents, substances utilized in the cosmetic industry, as well as in aesthetic and regenerative medicine. In this manuscript, we present a case of a 46-year-old female patient with multiple colored tattoos and a medical history of hypothyroidism and vulvar lichen sclerosus, who developed progressive musculoskeletal, neurological and cutaneous manifestations. Our study further emphasizes the critical need for differential diagnosis between ASIA syndrome and other immune-mediated pathologies, while advocating for enhanced clinical vigilance with thorough attention to the subjective examination, comprehensive review of prior medical conditions, and detailed assessment of potential exposure to adjuvants.

Keywords: Asia syndrome, tattoos, adjuvants, autoimmune diseases, genetic predisposition

Introduction

Definition of ASIA Syndrome

ASIA syndrome, or autoimmune/autoinflammatory syndrome induced by adjuvants, also known as Shoenfeld's syndrome after the immunologist who first described its symptoms in 2011, is a relatively new and little-known disease entity. In his work, he suggested creating a medical term as a common designation for conditions in which exposure to adjuvants, such as infectious pathogens, silicone, or aluminum salts, initiates autoimmune or autoinflammatory reactions in predisposed individuals.¹

From an immunological point of view, adjuvants are substances that activate pattern recognition receptors (PRR) of the innate immune system, used, among others, in vaccines to enhance the immune response to antigens (aluminum hydroxide). Beyond vaccines, adjuvants are commonly found in medicine and the cosmetics industry (silicone, hyaluronic acid (HA), polylactic acid, metal implants), as well as in nature as infectious agents (Epstein-Barr Virus, EBV) and toxic substances (mercury, crude oil). Despite the widespread presence of adjuvants in the environment, mainly genetically predisposed individuals are at risk of developing ASIA syndrome.²

Pathogenetic Basis of ASIA Syndrome

The essence of ASIA syndrome is the excessive activation of innate and adaptive immune mechanisms. Through hyperstimulation of macrophages, which play a crucial role in the innate immune response (as phagocytic cells and stimulators of CD8+ lymphocytes) and as antigen-presenting cells responsible for the maturation of Th1, Th2, and Th17

lymphocytes in adaptive immunity, it leads to an excessive autoinflammatory and autoimmune reaction, described as “Horror Autoinflammaticus and Autotoxicus”.³

The mechanism involves modulation of the activity of pattern recognition receptors, such as Toll-like receptors (TLR), NOD-like receptors (NLR), and C-type lectin receptors (CLR), which activate proinflammatory pathways, resulting in disruption of immune system homeostasis and stimulation of autoantibody production that can initiate or exacerbate autoimmune processes in genetically susceptible individuals.^{3,4}

Studies show a link between certain human leukocyte antigen (HLA) alleles and a higher incidence of ASIA syndrome in patients expressing these alleles. The most at-risk individuals carry HLA-DRB1 and HLA-B27 alleles, which are also typical for other autoimmune diseases like Reiter’s syndrome and ankylosing spondylitis.⁴

Another gene associated with ASIA syndrome is PTPN22 (protein tyrosine phosphatase non-receptor type 22), which encodes a protein regulating T and B lymphocyte activity in the specific immune response. Variants of this gene, especially single nucleotide polymorphisms (SNPs), lead to impaired immune function and dysregulation of immune responses.⁴

Original Assumptions of ASIA Syndrome

In their original work, Shoenfeld and Agmon-Levin described four disease syndromes that are similar in terms of clinical presentation and the pathophysiological phenomena underlying the observed symptoms. Based on these similarities, they proposed the creation of diagnostic criteria for ASIA syndrome.¹

One of the previously mentioned syndromes is macrophagic myofasciitis (MMF), described in 1998 in connection with vaccination against hepatitis B virus (HBV). It is characterized by chronic inflammation of the muscles and fascia, manifesting as pain and muscle weakness, which develops with the involvement of macrophages and granulomas formed as a reaction to aluminum-containing adjuvants.^{5–7}

Gulf War Syndrome (GWS), whose name comes from the symptoms of chronic fatigue, muscle and joint pain, as well as neurological disorders experienced by soldiers returning from the Gulf War, is also associated with exposure to adjuvants. However, it is not certain which substances directly contribute to the development of symptoms in patients; among the probable factors are squalene (present in anthrax vaccines), components of pesticides, and ammunition.^{5,7}

Sick Building Syndrome (SBS), as the name suggests, occurs in individuals who spend time in spaces contaminated by molds, fungi, and volatile organic compounds such as paints, solvents, and preservatives. These substances, acting as adjuvants, contribute to the development of complaints including headaches, fatigue, concentration disorders, respiratory tract irritation, and skin changes. The syndrome is chronic in nature and intensifies with continued exposure to harmful factors.^{5,8}

The last syndrome mentioned by Shoenfeld et al is Breast Implant Illness (BII). In genetically predisposed women, silicone breast implants can cause chronic activation of the immune system, leading to symptoms such as joint and muscle pain, chronic fatigue, cognitive disturbances, and skin and mucosal changes, which may occur both after implant damage or without any malfunction.⁵ Patients presenting with these symptoms usually meet at least two major diagnostic criteria for ASIA syndrome.⁹ In some women, due to the severity of symptoms implant removal is necessary, which is the most effective treatment method and usually leads to symptom resolution.^{5,9}

Case Report

A 46-year-old female patient was admitted to the Department of Dermatology due to suspected ASIA syndrome (Figure 1). In her medical history of chronic diseases, she reported hypothyroidism, treated with L-thyroxine at a dose of 25 µg/day, and vulvar lichen sclerosus (LS) diagnosed two years earlier. For the past seven years, the patient had been getting numerous tattoos, some of them colored, and additionally, seven years ago she underwent HA lip augmentation. The patient is an active tobacco smoker.

Therefore, among the known adjuvants to which the patient was exposed, tattoo pigments and presumably also HA fillers should be mentioned.

Evolution of Skin Lesions

The patient got her last tattoo in June 2022. She developed symptoms of contact allergy to the blue tattoo pigment (Figure 2), and after three months, she began to experience symptoms of livedo reticularis (Figure 3) and Raynaud’s

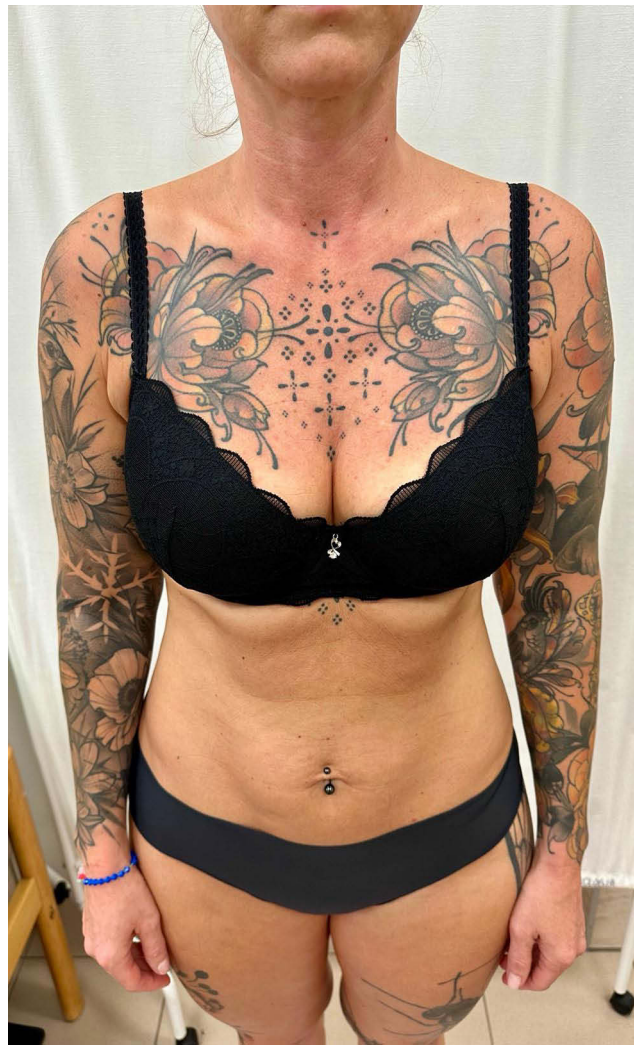


Figure 1 A 46-year-old woman with numerous tattoos, some of them colored.



Figure 2 Contact allergy to the blue tattoo pigment in our patient.



Figure 3 Symptoms of livedo reticularis in our patient.

phenomenon (Figure 4). The patient complained of fatigue and weakness, muscle pain, low-grade fever, difficulty falling asleep and staying asleep, memory problems, as well as itching and burning of the skin. Additionally, after several more months, the patient developed interstitial lung disease (in 2023), thus fulfilling the diagnostic criteria for ASIA syndrome.

Diagnostic Process

Considering the patient's medical history, it can be suspected that adjuvants in the form of tattoo pigments (particularly the blue pigment), which initiated inflammation as a contact reaction, as well as the activity of cofactors such as tobacco smoking (and possibly hyaluronic acid), led to the development of ASIA syndrome symptoms (Figure 5).

In addition to previously diagnosed hypothyroidism and vulvar lichen sclerosus (confirmed by histopathological examination), a diagnosis of interstitial lung disease was made after a pulmonology consultation. Neurological consultation revealed weakened reflexes in the upper limbs and absence of both knee reflexes.

As part of the diagnostic process, the patient underwent a series of laboratory, imaging, and functional tests. Biochemical tests revealed elevated inflammatory markers (CRP 30.7 mg/l). Serological tests showed antinuclear antibodies (ANA) at a titer of 1:160, a negative immunoblot, and no monoclonal protein in serum protein immunofixation. The Schirmer test confirmed dry eye syndrome, while patch tests showed contact allergy to cobalt. Echocardiography revealed minor fibrosis on the anterior leaflet of the mitral valve and the right leaflet of the aortic



Figure 4 Raynaud's phenomenon in our patient.

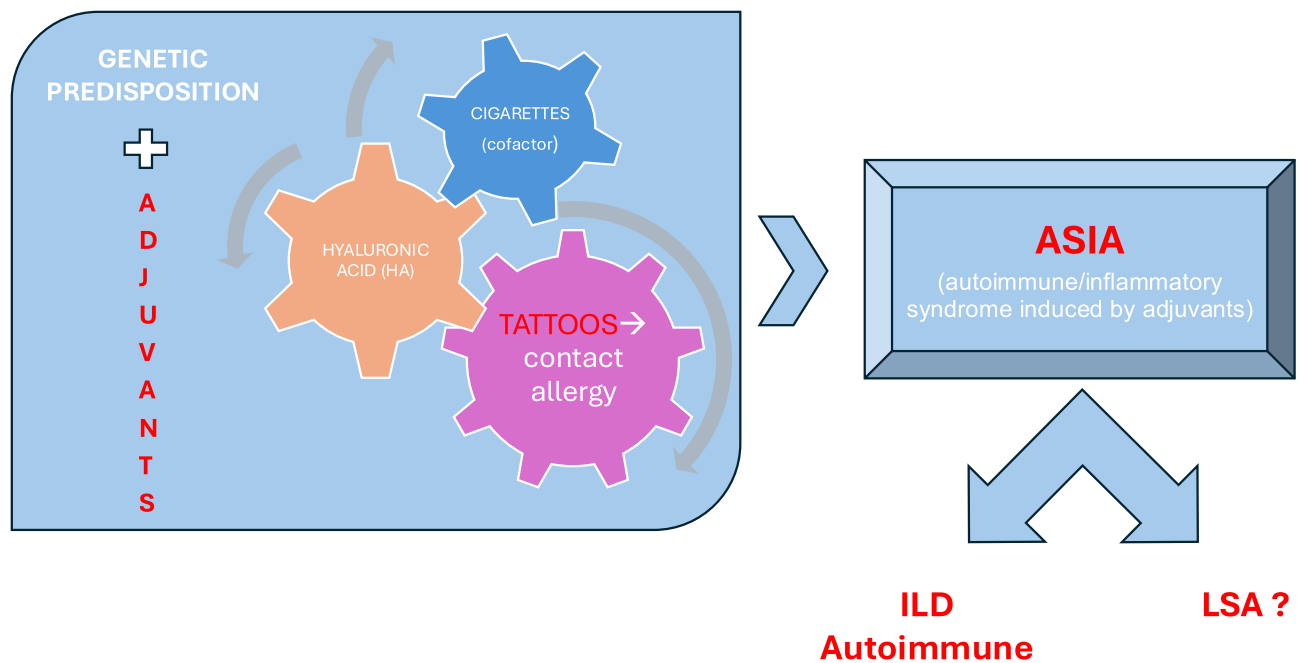


Figure 5 A probable scheme of ASIA syndrome development in the patient, considering possible causative factors and consequences.^{10,11}

valve, without disturbances in wall thickness or contractility. Abdominal and chest CT scans described nonspecific nodules scattered in the parenchyma of both lungs and interstitial consolidations. Capillaroscopy, head MRI, and angio-MRI with and without contrast were normal. Doppler ultrasound of the carotid arteries did not show significant hemodynamic stenosis.



Figure 6 Symptoms of Ascher's syndrome in our patient.

Additionally, the patient presents with symptoms of Ascher's syndrome, which is associated with autoimmune thyroid disorders. She exhibits signs of blepharochalasis (so-called edematous eyelid laxity) and a double lip fold (Figure 6). The thyroid ultrasound revealed nodules that were qualified for biopsy.

Given and Planned Treatment

The patient received treatment with hydroxychloroquine (HCQ). Incorporation of mycophenolate mofetil (MMF) into the therapeutic protocol is also scheduled, depending on the decision of the pulmonary specialist.

Discussion

Clinical Presentation of ASIA Syndrome

The diagnostic criteria for ASIA syndrome, proposed in 2011 by Shoenfeld et al and modified by Watad et al in 2017, are divided into so-called major and minor criteria. A detailed list of symptoms is presented in Table 1. The diagnosis of ASIA syndrome is possible after fulfilling at least two major criteria or one major and two minor criteria.^{1,2} Our patient

Table 1 ASIA Syndrome Diagnostic Criteria – Modified After.

Major Criteria	Minor Criteria
1. Exposure to external factors such as: <ul style="list-style-type: none"> ● infection, ● vaccine, ● silicone, ● adjuvant*, preceding the onset of clinical symptoms	1. The appearance of autoantibodies or antibodies directed against the suspected adjuvant.
2. The appearance of "typical" clinical symptoms: <ul style="list-style-type: none"> ● myalgia*, myositis, or muscle weakness*, ● arthralgia and/or arthritis, ● chronic fatigue*, unrefreshing sleep, or sleep disturbances*, ● neurological symptoms (especially related to demyelination) – cognitive impairment, memory loss*, ● fever, dry mouth, dry eye syndrome* 	2. Other clinical symptoms (eg, irritable bowel syndrome)

(Continued)

Table 1 (Continued).

Major Criteria	Minor Criteria
3. Removal of the triggering factor leads to improvement in symptoms	3. Specific HLA types (eg, HLA DRB1, HLA DQB1)
4. Typical biopsy of the affected organs	4. Development of autoimmune disease* (eg, MS, SSc) – in our patient ILD*

Note: *The criteria fulfilled by the patient. Adapted from *J Autoimmun*, volume 36(1). Shoenfeld Y, Agmon-Levin N. 'Asia' - autoimmune/inflammatory syndrome induced by adjuvants. 4–8, copyright 2011, with permission from Elsevier.¹

Abbreviations: SM, sclerosis multiplex; SSc, systemic sclerosis; HLA, human leukocyte antigens; ILD, interstitial lung disease.

met the following criteria. The symptoms included in the major criteria are rather non-specific but occur very frequently in affected individuals. Arthralgia affects nearly three-quarters of patients, and over 60% experience symptoms of chronic fatigue. About half of patients diagnosed with ASIA syndrome report muscle pain and general weakness.¹² One third of patients present with neurological symptoms and cognitive disorders, as well as fever and lymphadenopathy.¹²

In our patient, muscle complaints and weakness are so severe that, as a physical education teacher, she is unable to work.

In laboratory tests of patients diagnosed with ASIA syndrome, non-specific abnormalities can be expected, such as elevated levels of C-reactive protein (CRP) as well as ACE and soluble IL-2R, with values above the upper limit of normal observed in about 50% of patients. Anemia and polyclonal hypergammaglobulinemia are also relatively common. For differential diagnosis with other disease entities, it is useful to determine TSH levels, vitamin D3, and muscle enzyme activity.¹³

In serological tests, antinuclear antibodies (ANA) are present in one in five patients, while among other specific antibodies, the following may be positive: anti-SSA/SSB, anti-dsDNA, anti-Scl-70, anti-cardiolipin, anti-CCP antibodies, IgM rheumatoid factor, cryoglobulins, and/or anti-neutrophil cytoplasmic antibodies (ANCA).¹³

Functional tests can help to objectify the symptoms reported by patients. The Schirmer test may reveal an abnormal tear film breakup time and corneal epithelial defects, whereas in patch tests performed due to frequently suspected contact dermatitis, the result is usually negative.^{13,14} For the diagnosis of symptoms such as chronic weakness and fatigue, echocardiography may be helpful; in most cases, it shows good systolic function of the left ventricle with mild mitral regurgitation.¹⁵

In 2023, Cohen Tervaert et al, based on an analysis of numerous case reports of patients presenting with ASIA syndrome symptoms, suggested including the presence of small fiber neuropathy (SFN) and anti-GPCR autoantibodies (autoantibodies against G protein-coupled receptors) in the diagnostic criteria.^{16,17} Characteristic features of SFN include neuropathic pain and symptoms related to the autonomic nervous system, such as fatigue, anxiety, and depression. The basis of this pathology is structural damage to thin myelinated A-delta fibers and unmyelinated C fibers in the distal nerve endings.^{16,18} The pain and burning (“tingling”) sensation of the skin reported by our patient may be due to SFN. This symptom is quite characteristic in such patients, and confirmation can be obtained by a skin biopsy showing reduced intraepidermal nerve fiber density and/or abnormal temperature threshold.

Soriano et al identified four groups of patients most at risk for developing ASIA syndrome. Medical history information indicating increased risk of this syndrome includes previous post-vaccination reactions, a history of severe allergic reactions, individual predisposition to autoimmunity, and other predispositions, including genetic factors (HLA-DR4, DRB1, DR53, DQA1*0102), the presence of autoantibodies, and a strong family history of autoimmune diseases.^{5,19}

Among the symptoms seen in patients that may indicate an increased risk of developing ASIA syndrome are, among others, Raynaud’s phenomenon (appearing de novo, which in our patient can also be triggered by the underlying diagnosis of vulvar lichen sclerosus), alopecia areata and telogen effluvium, recurrent urticaria and other poorly defined skin lesions, as well as unexplained pruritus and symptoms suggesting small fiber neuropathy (pain, burning, tingling).⁵

Watad et al, based on data from the International ASIA Syndrome Registry from 2016–2019, assessed the pattern of coexistence of other immunological diseases in patients.¹² Disease entities were divided into three groups: autoimmune diseases, autoinflammatory diseases, and those of intermediate character.

Autoimmune diseases included, among others: ANCA-associated vasculitis, rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus (SLE), undifferentiated connective tissue disease (UCTD), systemic sclerosis (SSc), morphea (localized scleroderma, LoSc), multiple sclerosis (MS), and type 1 diabetes mellitus (DM1). Autoinflammatory diseases included, among others: giant cell arteritis, Still's disease, and inflammatory bowel diseases. Diseases of mixed character, for the purposes of the study, included ankylosing spondylitis, Behçet's disease, as well as psoriasis and psoriatic arthritis.^{12,16}

Concerning findings have emerged from studies on the impact of adjuvants on the neoplastic transformation of lymphocyte cells. Chronic stimulation of the immune system through various mechanisms, such as effects on cellular DNA or uric acid production, induces inflammation and increases the risk of genetic aberrations, thus leading to the development of lymphomas.^{16,20} A particular focus in this research is the increased incidence of anaplastic large-cell lymphoma (ALCL) in patients with breast implants.^{16,21} In a 2018 study by de Boer et al, among 43 patients with anaplastic large-cell lymphoma, 32 had breast implants on the side affected by the disease.²¹ Other neoplastic complications include EBV-positive large B-cell lymphomas, intravascular large B-cell lymphomas, and squamous cell carcinoma (SCC). Nevertheless, life-threatening complications of breast implants are rare, with the most common being implant rupture and leakage, while malignant changes remain uncommon.^{21–23}

Treatment

In the case of nonspecific symptoms of ASIA syndrome, such as fatigue, sleep disturbances, cognitive impairment, musculoskeletal pain, and arthritis, analgesic treatment is recommended, using nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticosteroids (GCS) (0.5–1 mg/kg). However, persistent and severe symptoms are an indication for the initiation of steroid therapy in combination with antimalarial and immunosuppressive drugs (cyclosporine, tacrolimus, azathioprine, methotrexate, mycophenolate mofetil).²⁴

If a patient with symptoms of ASIA syndrome is diagnosed with another autoimmune disease, treatment should be conducted according to the guidelines for that particular disease entity. There is no doubt that, due to the multitude and diversity of symptoms, patients require a holistic and multidisciplinary approach to both diagnosis and treatment, including psychotherapeutic management in patients with psychological symptoms. The basis of treatment in every case where the adjuvant factor is known is its removal; however, this does not always result in improvement of the patient's clinical condition.²⁴

Diagnostic Vigilance - Adjuvants

Due to the multitude of substances that can act as adjuvants and contribute to the development of ASIA syndrome, diagnostic vigilance among physicians of various specialties is essential in everyday practice. The key factor in identifying patients predisposed to developing ASIA syndrome is a thorough medical history, with particular attention to exposure to factors that may trigger this syndrome.

In the field of aesthetic and regenerative medicine, numerous bioimplants containing hyaluronic acid, polylactic acid, acrylates, silicones, or tattoo pigments are considered risk factors, as in the case of our patient. Classic medical implants, such as breast implants, testicular implants, hernia meshes, slings used in the treatment of urinary incontinence, intrauterine devices, and dental implants, should also be considered during patient history taking. Among infectious factors, both direct infection (eg, with SARS-CoV-2) and vaccine components (including those against COVID-19, influenza, human papillomavirus (HPV), and hepatitis B virus (HBV)), also due to their aluminum salt content, may predispose to the development of autoimmune and autoinflammatory reactions via the ASIA syndrome mechanism.¹⁶

Tattoo pigments, especially colored and inorganic ones, may contain chemical compounds with increased levels of heavy metals. Aluminum compounds present in blue pigment can trigger ASIA syndrome in predisposed individuals. On the other hand, currently more commonly used organic pigments are primarily composed of condensed aromatic amines, which have carcinogenic and allergenic effects.²⁵ Contrary to frequently repeated slogans, colored pigments have not

been banned, but additional restrictions have been introduced regarding the composition and concentration of substances such as azo dyes, aromatic amines, polycyclic aromatic hydrocarbons, metals, and methanol. Limiting their concentration is intended to minimize the risk of adverse effects in tattooed individuals.²⁶

The Role of Tattoos in the Pathogenesis of ASIA Syndrome

Tattoo ink is a suspension of insoluble pigments in a liquid, which consists of solvents and various additives. Soluble dyes are not suitable for the production of tattoo inks due to their susceptibility to degradation. Therefore, pigments are used in inks; these are insoluble and are divided into three main groups: organic, inorganic, and carbon black.²⁷

The skin serves a protective function, acting as a barrier against various external factors. It is responsible for maintaining the body's internal balance and for receiving sensory stimuli. In a study on the effect of tattoo ink on interstitial fluid, a sensor called a biosensor was used, placed in the dermis layer, which contains collagen, elastin fibers, and glycosaminoglycans. This layer contains fibroblasts responsible for tissue construction and regeneration, immune cells - macrophages, as well as adipocytes that serve a storage function. Small soluble ink particles penetrate blood or lymphatic vessels, from where they are transported to various organs, where they may be stored or eliminated from the body. In contrast, larger insoluble particles that are not absorbed or distributed are retained in vacuoles, called melanosomes, present in the cytoplasm of dermal macrophages.²⁷

Most colored inorganic pigments contain iron oxides. Iron ore often contains heavy metals such as nickel, whose chemical compounds are classified as carcinogenic by the International Agency for Research on Cancer (IARC). The European rapid alert system for dangerous substances (RAPEX) reports that 28% of tattoo inks showed heavy metal content exceeding the threshold values set by the Council of Europe Resolution (CoE ResAP) (2008). The alerts primarily concerned nickel, arsenic, barium, cadmium, chromium (VI), copper, lead, and zinc.²⁵ However, currently, over 80% of coloured pigments are of organic origin. These include colours ranging from yellow to red. They are composed of condensed aromatic amines, which are often carcinogenic or allergenic substances.²⁵

Due to the inevitable skin damage caused by the tattoo needle, infections caused by microorganisms that can enter the resulting wound are not uncommon. The manifestation of allergic reaction symptoms can begin not only during wound healing but also many months or even years after the wound has healed. This situation creates diagnostic difficulties in identifying the specific component causing the reaction.²⁵

Among non-allergic reactions, cutaneous pseudolymphomas can be distinguished, whose pathogenesis remains unknown. They constitute a group of benign reactive lymphoproliferative processes of T or B cells that clinically and histologically mimic cutaneous lymphoma. Tattooing can also trigger dermatoses such as psoriasis, lichen planus, cutaneous lupus erythematosus, and pyoderma gangrenosum associated with the Koebner isomorphic phenomenon.²⁵

Several individual cases of hypersensitivity reactions to tattoos associated with the production of antibodies have been described. An example is a woman who developed urticaria and symptoms of an IgE-mediated reaction to certain pigments—purple and blue—confirmed by skin tests after adding color to her tattoo.²⁵ On the other hand, aluminum compounds, which are components of blue tattoo pigment, have a proven association with ASIA syndrome.

Conclusions

Autoimmune/autoinflammatory syndrome induced by adjuvants, as a complex, multifactorial, and multisymptomatic disease entity, poses a diagnostic challenge that requires a multidisciplinary approach and diagnostic vigilance, especially in the area of medical history taking. The simultaneous occurrence of atypical skin, joint, muscle, and neurological symptoms in patients exposed to adjuvants—through aesthetic or regenerative medicine procedures or certain vaccinations—should always prompt differential diagnosis with ASIA syndrome. The case of our patient may serve as an example demonstrating the multiplicity of substances that can act as adjuvants, especially in the field of aesthetic cosmetics.

Ethics and Consent Statements

Written informed consent for publication has been secured from the patient. The patient provided informed consent to publish case details and any accompanying images. Ethics committee approval was not required, as in accordance with Polish law, the patient provided explicit consent for the use of her image for scientific purposes.

Disclosure

The authors report no conflicts of interest in this work.

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