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Tattoo as a Possible Trigger for Autoimmune Syndrome Induced by Adjuvants

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Tattoo as a Possible Trigger for Autoimmune Syndrome Induced by Adjuvants

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Abstract- **Autoimmune/Inflammatory Syndromes Induced by Adjuvants (ASIA) syndrome is a group of immune-mediated disorders and symptoms that may appear in genetically predisposed individuals after environmental exposure to external factors, the adjuvants, such as silicone, aluminium and other metals. Sarcoidosis, one of its classic examples, have been previously described following tattoo. However, tattoo ink is still not recognized as one of the adjuvants capable of triggering the ASIA syndrome. To reinforce our theory, we also described a 32-year-old patient that developed arthralgia, sicca syndrome, small fiber neuropathy, and post orthostatic tachycardia syndrome (POTS) after being exposed to extensive areas of tattoos and propose the tattoo ink as a possible trigger for the ASIA syndrome, questioning its safety in individuals genetically prone for autoimmunity.**

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I. Introduction

Autoimmune/Inflammatory Syndromes Induced by Adjuvants (ASIA) comprise a group of immune-mediated disorders that flourish in genetically predisposed individuals after environmental exposure to so-called adjuvants [1]. The most described adjuvants related to this syndrome include silicone (i.e. Breast silicone implants), aluminium salts, and other metals and vaccines [2–6]. The removal of these agents tend to lead to an improvement of the symptoms and reduction of the related autoantibodies levels when present [5–7]. The adjuvants are responsible for stimulating both the innate and the adaptive immune system and for activating pattern recognition receptors, increasing the immune response to non-pathological stimuli in a genetically prone subject[8].

Sarcoidosis, Sjogren's syndrome, silicone implant incompatibility, and undifferentiated connective tissue disease (UCTD) are examples of conditions that could be considered to have a common pathogenic mechanism for ASIA syndrome, in which individuals genetically prone to autoimmunity, such as those with HLADRB1 or having the PTPN22 genes, develop the disorder after being exposed to the external triggers[9–11].

II. Case in Point

A 32-year-old woman presented with arthralgia in her both wrists, knees and ankles, pain in the Achilles tendon area and morning stiffness of one to two hours everyday, dry mouth and eyes, generalized fatigue, right hand and right hemifacial weakness and hyperesthesia of the right leg that appeared two months ago. She had no fever or skin rashes. Additionally, she complains of headache and blurred vision that started around four months ago, with no photophobia or nausea and vomiting, as well as tachycardia and dizziness when standing up. Her physical examination had no remarkable findings, orthostatic hypotension test was negative, but tachycardia of 125 bpm was detected during the maneuver. On her laboratory examination, she had no outstanding results, including low inflammatory phase markers on her blood and negative ANA, anti-Ro, anti-La and ANCA. Her sacral MRI shows no signs of acute or chronic sacroiliitis or findings compatible with spondyloarthritis, her regular and angio-CT of the head were normal, as well as lumbar puncture (LP). On her brain MRI there was no acute findings, and she was treated with IV hydration and caffeine with partial response. To evaluate her peripherical neurological complaints, a Nerve Conduction Study Electromyogram (NCS-EMG) was performed showing a decreased sympathetic response on her right foot and normal on her right hand, with no signs of large fiber polyneuropathy or radiculopathy, that may be compatible with small fiber neuropathy, requiring a skin biopsy for confirmation. When looking for circulating autoantibodies against G protein-coupled receptors of the autonomic nervous system, she had high levels of antibodies against beta1adrenergic receptor, Beta 2 adrenergic receptor and M3 acetylcholine receptor.

On her medical background, she had a previous diagnosis of Crohn's disease (CD), made two years ago, when she had fatigue, generalized arthralgia and diarrhea, positive Anti-saccharomyces cerevisiae antibodies, colonoscopy and capsule endoscopy with signs of inflammation in the terminal ileum and confirming biopsy for CD. At the time, it was started treatment with Prednisone 40 mg, with partial

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improvement. Biological therapy with Vedolizumab was recommended, but the patient refused the treatment. She had no CD symptoms until four months ago when she had disease flare with diarrhea and abdominal pain, treated with steroids. In addition to CD, her past medical history is positive for depression and anxiety, treated with selective serotonine receptor inhibitor, endometriosis and deep venous thrombosis in her right arm in 2017, treated with clexane for three months.

The patient works as a tattoo artist and has personally done extensive tattoos on her own (Fig. 1-4). Before her tattoos, she had no symptoms.

a) Aluminium and other metals and tattoo

Interestingly, aluminium salts and other metals were described as components of different colors of tattoo ink [30]. Specifically, the aluminium salts were described as ingredients of the violet ink. Our patient, that had no symptoms previous to her fist tattoo, has various and extensive tattoos, including some with violet ink (Fg. 1-4). The presence of aluminium in ink could explain the mechanism through which tattoo may lead to ASIA syndrome, as observed in the described patient.

b) Sjogren's syndrome and Tattoo

Sjogren's syndrome (SS) is an autoimmune condition in which salivary and lacrimal glands inflammation lead to a glandular dysfunction, resulting clinically in dry eyes and mouth and commonly other extra-glandular manifestations, including arthralgia [12]. It can be primary or secondary to other autoimmune conditions, such as rheumatoid arthritis [12]. Our patient presented to us with generalized arthralgia, as well as dry mouth and eyes with a positive Schirmer test. Even though SS is considered one of the classic examples of ASIA syndrome[9], there are no reports in the literature that associate those symptoms with the presence of tattoo pigments. Sarcoidosis, on the other hand, another classic manifestation of ASIA syndrome, had been previously associated with the presence of tattoos[13–15].

c) Sarcoidosis and Tattoo

Sarcoidosis is a systemic granulomatous pathology of still unclear etiology that develops when a prone individual is exposed to an antigen capable of inducing Th1 immune response and consequent granuloma formation in different organs, including mainly the lungs and lymph-nodes [16]. Infections, autoantigens and inorganic compounds were already described as common triggers[17]. A 29-year-old man had been reported to develop systemic sarcoidosis after tattoo. He had pleuritic chest pain, dyspnoea and cough. On physical examination, there were papules over his tattoo areas and bilateral basal crackles on lung auscultation. Chest X-ray showed bilateral lymphadenopathy and reticulonodular opacities. In the skin biopsy, noncaseating granulomas with black tattoo pigments were observed[15].

Systemic sarcoidosis and granulomatous reaction without sarcoidosis were previously described in more than 30 patients following permanent tattoo, in the presence or absence of uveitis [13].It is well known that sarcoidosis granulomas tend to develop in previous scars sites, explaining the finding of granulomas in the tattoo areas in those patients [15].Interestingly, three tattooedpatients were described with isolated eye inflammation, which included posterior uveitis, panuveitis and retinal vasculitis, without other manifestations or granuloma formation elsewhere [18–20].This may suggest that tattoo ink contains a specific antigen that could stimulate the immune response, locally seen by granuloma formation in the tattoo area or other systemic inflammatory manifestations such as uveitis. A vitreous biopsy performed in a patient with tattoo-associated uveitis showed no tattoo pigment or granulomas, but infiltration ofT-lymphocytes with atypia, supporting the explanation of this symptom occurring due to an autoinflammatory/immune reaction [21].

d) Post Orthostatic Tachycardia syndrome, ASIA syndrome and tattoo

Our patient also presented with tachycardia and dizziness when standing up. Post-orthostatic Tachycardia syndrome (POTS) is a clinical condition in which patients present with tachycardia and discomfort symptoms when assuming the orthostatic position, without hypotension. The orthostatic tachycardia is described as an elevation of 30 bpm from the heart rate measured before standing or maintaining the heart rate, within 10 minutes of standing, superior of 120bpm[22]. The symptoms include palpitations, lightheadedness, blurred vision, generalized weakness, fatigue, among others. The physiopathology of POTS combines multiple and coexistent mechanisms, such as autonomic denervation, hypovolemia and hyperadrenergic stimulation [23]. Although its etiology remains unclear, many studies had recently supported the hypothesis of it being an autoimmune disease[24]. The central argument for this hypothesis is the finding of autoantibodies in POTS patients' sera. These antibodies mainly target G-coupled proteins, including muscarinic, nicotinic and adrenergic receptors[24–27]. POTS was previously associated with small fiber neuropathy and, thus, may also be a part of ASIA syndrome. In Germany, C fiber involvement was observed in 45% of the 84 patients with POTS analyzed – and the reduced density of those fibers was correlated with a decreased adrenergic cardiac 123 I-metaiodobenzylguanadine (MIBG) uptake – suggesting an association between the small fiber neuropathy and the reduced myocardial postganglionic sympathetic innervation that could explain the abnormal tachycardia in those patients[28]. Other researchers looked for the correlation between

POTS and SFN. It was found that 20% of POTS patients' skin biopsy had signs of SFN[29].

e) Similarities between Silicone Incompatibility Syndrome and ASIA syndrome following tattoo

Recently, silicone breast implants were associated with the development of many general symptoms, for example, sleep disturbances, general fatigue, generalized pain, depression, hair loss, among others [9]. It has been proposed that those symptoms may relate to an autoimmune neurosensory dysautonomia, involving autoantibodies against G-protein coupled receptors of the autonomic nervous system such as the adrenergic and endothelin and angiotensin ones, which may result in small fiber neuropathy in a subgroup of these women [31]. Similarly, our patient had depression, anxiety and multiple neurologic complaints with an NCS-EMG showing decreased sympathetic response on her right foot, with no signs of large fiber polyneuropathy.

As for the above mentioned, autonomic-related manifestations (POTS, sicca syndrome, paresthesia and other signs of small fiber neuropathy) reported by our patient, we hypothesized the potential involvement of autoantibodies against GPCRs of the autonomic nervous system. These functional antibodies have already been described to be involved in the development of autoimmune diseases and other suspected immune- and dysautonomic-related disorders (such as Sjögren's syndrome, RA, SLE, MS, myasthenia gravis, POTS etc.[32–38]) and were found to be dysregulated in women with SBIs as well (Submitted/Personal communication). Indeed, we found increased circulation levels of anti-beta1, anti-beta2 and anti-M3 AAbs in our patient as compared to the normal ranges in healthy women, which might play a role in the appearance of autonomic-related symptoms in our patient.

f) Potential therapies for ASIA syndrome following tattoo

Some cases of ASIA syndrome had also been described following injection of S.C. methylmetacrylate [39–41]. Methylmetacylate S.C. injections have been used in the last decades mainly with aesthetic goals in different body areas, from the lips to the buttocks. It has been recently proposed to treat those patients with intralesional neodymium laser [42]. Intralesional laser technique has been largely used as well for tattoo removal [43, 44]. As previously mentioned, frequently, in ASIA syndrome, the removal of the adjuvant exposure may ameliorate the signs and symptom of the disease. Extraction of silicone implants, for instance, was shown to improve the symptoms such as fatigue, arthralgia and sicca syndrome [45]. Hence, tattoo laser removal could be a potential treatment option for those patients.

III. Conclusion

In this review, we raise the hypothesis of tattoo pigment as a new component of the group of adjuvants that trigger ASIA syndrome and question its safety in individuals genetically prone to develop autoimmunity. To reinforce our proposal, we described a 32-year-old woman with known Chron's disease that presented with arthralgia, morning stiffness, dry mouth and eyes, POTS and neurological complaints compatible with small fiber neuropathyafter exposure to an extensive tattoo pigmentation (Fg 1-4). Although those symptoms had not been previously associated with the presence of tattoo ink, permanent tattoos had been previously linked to sarcoidosis and isolated uveitis [15, 46]. In addition, those symptoms have been related to other environmental exposures, such as to aluminium, other metals, silicone and vaccines [1, 6, 7, 9, 47].In fact, some of the tattoo inks have been demonstrated to contain aluminum [30]. Moreover, removing the adjuvants had been shown to improve the clinical presentation and the laboratory markers in ASIA syndrome [9]. Tattoo removal with laser technique could be a potential solution for ASIA syndrome following tattoo.

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Figures 1-4: Images from our patient's extensive tattoos.

References Références Referencias

1. Shoenfeld Y, Agmon-Levin N (2011) "ASIA"-autoimmune/inflammatory syndrome induced by adjuvants. J Autoimmun 36:4–8.
2. Molina V, Shoenfeld Y (2005) Infection, vaccines and other environmental triggers of autoimmunity. Autoimmunity 38:235–245.
3. Inbar R, Weiss R, Tomljenovic L, Arango M-T, Deri Y, Shaw CA, Chapman J, Blank M, Shoenfeld Y (2017) Behavioral abnormalities in female mice following administration of aluminum adjuvants and the human papillomavirus (HPV) vaccine Gardasil. Immunol Res 65:136–149.
4. Nancy A-L, Shoenfeld Y (2008) Chronic fatigue syndrome with autoantibodies--the result of an augmented adjuvant effect of hepatitis-B vaccine and silicone implant. Autoimmun Rev 8:52–55.
5. Kagan P, Halpert G, Amital H, Shapira R, Shoenfeld Y (2020) Autoimmune/Inflammatory Syndrome Induced by Adjuvant Associated with a Metal Implant in the Mouth; Explantation Was Followed by Recovery. Isr Med Assoc J 9:516–517.
6. Schiff A, Jiries N, Goldsztein S, Schiff E, Ginsberg S (2020) A possible association of orthopedic metal implants and ASIA syndrome. Rheumatology (Oxford). https://doi.org/10.1093/rheumatology/keaa481

7. Watad A, Sharif K, Shoenfeld Y (2017) The ASIA syndrome: basic concepts. Mediterr J Rheumatol 28:64–69
8. Watad A, Quaresma M, Brown S, Cohen Tervaert JW, Rodríguez-Pint I, Cervera R, Perricone C, Shoenfeld Y (2017) Autoimmune/inflammatory syndrome induced by adjuvants (Shoenfeld's syndrome) - An update. Lupus 26:675–681.
9. Borba V, Malkova A, Basantsova N, Halpert G, Andreoli L, Tincani A, Amital H, Shoenfeld Y (2020) Classical Examples of the Concept of the ASIA Syndrome. Biomolecules 10:1436.
10. Cárdenas-Roldán J, Rojas-Villarraga A, Anaya J-M (2013) How do autoimmune diseases cluster in families? A systematic review and meta-analysis. BMC Med 11:73.
11. Steiner S, Becker SC, Hartwig J, Sotzny F, Lorenz S, Bauer S, Löbel M, Stittrich AB, Grabowski P, Scheibenbogen C (2020) Autoimmunity-Related Risk Variants in PTPN22 and CTLA4 Are Associated With ME/CFS With Infectious Onset. Front Immunol 11:578.
12. Mariette X, Criswell LA (2018) Primary Sjögren's Syndrome. N Engl J Med 378:931–939.
13. Kluger N (2018) Tattoo-associated uveitis with or without systemic sarcoidosis: a comparative review of the literature. J Eur Acad Dermatol Venereol 32:1852–1861.
14. Izumikawa K, Motoi N, Takaya H, Miyamoto A, Eishi Y, Yoshimura K, Kishi K (2011) A case of concurrent sarcoidosis, aortitis syndrome and Crohn's disease. Intern Med 50:2915–2917.
15. Torres LK, Faiz SA (2014) Tattoos and Sarcoidosis. N Engl J Med 370:e34.
16. Bindoli S, Dagan A, Torres-Ruiz JJ, Perricone C, Bizjak M, Doria A, Shoenfeld Y (2016) Sarcoidosis and Autoimmunity: From Genetic Background to Environmental Factors. Isr Med Assoc J 18: 197–202.
17. Valeyre D, Prasse A, Nunes H, Uzunhan Y, Brillet P-Y, Müller-Quernheim J (2014) Sarcoidosis. Lancet (London, England) 383:1155–1167.
18. Orellana Rios J, Verdaguer Díaz JI, Agee J, Theodore Smith R (2018) Tattoo associated retinochoroiditis. Arch Soc Esp Oftalmol 93: 193–197.
19. Klímová A, Heissigerová J, Říhová E, Holan P, Brichová M, Svozílková P (2017) [TATTOO-ASSOCIATED UVEITIS]. Ces a Slov Oftalmol Cas Ces Oftalmol Spol a Slov Oftalmol Spol 73:30–33.
20. Moschos MM, Guex-Crosier Y (2004) Retinal vasculitis and cystoid macular edema after body tattooing: a case report. Klin Monbl Augenheilkd 221:424–426.
21. Reddy AK, Shildkrot Y, Newman SA, Thorne JE (2015) T-Lymphocyte Predominance and Cellular Atypia in Tattoo-Associated Uveitis. JAMA Ophthalmol 133:1356–1357.
22. Sheldon RS, Grubb BP 2nd, Olshansky B, et al (2015) 2015 heart rhythm society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. Hear Rhythm 12:e41-63.
23. Benarroch EE (2012) Postural tachycardia syndrome: a heterogeneous and multifactorial disorder. Mayo Clin Proc 87:1214–1225.
24. Li H, Yu X, Liles C, et al (2014) Autoimmune basis for postural tachycardia syndrome. J Am Heart Assoc 3:e000755.
25. Gunning 3rd WT, Kvale H, Kramer PM, Karabin BL, Grubb BP (2019) Postural Orthostatic Tachycardia Syndrome Is Associated With Elevated G-Protein Coupled Receptor Autoantibodies. J Am Heart Assoc 8:e013602–e013602.
26. Fedorowski A, Li H, Yu X, et al (2017) Antiadrenergic autoimmunity in postural tachycardia syndrome. Europace 19:1211–1219.
27. Dubey D, Hopkins S, Vernino S (2016) M1 and M2 muscarinic receptor antibodies among patients with postural orthostatic tachycardia syndrome: potential disease biomarker. J Clin Neuromuscul Dis 17:179S.
28. Haensch C-A, Tosch M, Katona I, Weis J, Isenmann S (2014) Small-fiber neuropathy with cardiac denervation in postural tachycardia syndrome. Muscle Nerve 50:956–961.
29. Iodice V, Low DA, Mathias CJ, Facer P, Yiangou Y, Anand P (2015) Small fibre neuropathy and collagen IV reduction in postural tachycardia syndrome and joint hypermobility syndrome. Auton Neurosci 192:125.
30. Islam PS, Chang C, Selmi C, Generali E, Huntley A, Teuber SS, Gershwin ME (2016) Medical Complications of Tattoos: A Comprehensive Review. Clin Rev Allergy Immunol 50:273–286.
31. Shoenfeld Y, Ryabkova VA, Scheibenbogen C, et al (2020) Complex syndromes of chronic pain, fatigue and cognitive impairment linked to autoimmune dysautonomia and small fiber neuropathy. Clin Immunol 214:108384.
32. Park K, Haberberger R V, Gordon TP, Jackson MW (2011) Antibodies interfering with the type 3 muscarinic receptor pathway inhibit gastrointestinal motility and cholinergic neurotransmission in Sjögren's syndrome. Arthritis Rheum 63:1426–1434.
33. Malysheva O, Pierer M, Wagner U, Wahle M, Wagner U, Baerwald CG (2008) Association between beta2 adrenergic receptor polymorphisms and rheumatoid arthritis in conjunction with human leukocyte antigen (HLA)-DRB1 shared epitope. Ann Rheum Dis 67:1759–1764.

34. Jazdzewski K, Bednarczuk T, Stepnowska M, Liyanarachchi S, Suchecka-Rachon K, Limon J, Narkiewicz K (2007) beta-2-adrenergic receptor gene polymorphism confers susceptibility to Graves disease. Int J Mol Med 19:181–186.
35. Metcalf J V, Bhopal RS, Gray J, Howel D, James OF (1997) Incidence and prevalence of primary biliary cirrhosis in the city of Newcastle upon Tyne, England. IntJEpidemiol 26:830–836.
36. Cabral-Marques O, Marques A, Giil LM, et al (2018) GPCR-specific autoantibody signatures are associated with physiological and pathological immune homeostasis. Nat Commun 9:5224.
37. Xu BY, Huang D, Pirskanen R, Lefvert AK (2000) beta2-adrenergic receptor gene polymorphisms in myasthenia gravis (MG). Clin Exp Immunol 119:156–160.
38. Smith AJ, Jackson MW, Wang F, Cavill D, Rischmueller M, Gordon TP (2005) Neutralization of muscarinic receptor autoantibodies by intravenous immunoglobulin in Sjögren syndrome. Hum Immunol 66:411–416.
39. Vera-Lastra O, Rojas-Milán E, Peralta-Amaro AL, Sánchez-Uribe M, Cruz-González LI, Hernández-Sánchez M, Tecayehuatl-Negrete L, Cruz-Dominguez MDP, Jara LJ (2020) Autoimmune/inflammatory syndrome induced by methylmethacrylate associated to seronegative antiphospholipid syndrome and diffuse large B-cell non-Hodgkin's lymphoma. Lupus 29:1292–1296.
40. Goldman A, Wollina U (2019) Polymethylmethacrylate-induced nodules of the lips: Clinical presentation and management by intralesional neodymium: YAG laser therapy. Dermatol Ther 32:e12755.
41. Goldman A, Staub H, Wollina U (2018) HYPERCALCEMIA DUE TO POLYMETHYLMETHACRYLATE INJECTIONS? (LITERATURE REVIEW AND CASE REPORTS). Georgian Med News 17–20
42. Goldman A, Wollina U (2018) Intralesional Neodymium YAG laser to Treat Complications of Polymethylmethacrylate. Open access Maced J Med Sci 6:1636–1641.
43. Ahn KJ, Zheng Z, Kwon TR, Kim BJ, Lee HS, Cho S Bin (2017) Pattern analysis of laser-tattoo interactions for picosecond- and nanosecond-domain 1,064-nm neodymium-doped yttrium-aluminum-garnet lasers in tissue-mimicking phantom. Sci Rep 7:1533.
44. Khunger N, Molpariya A, Khunger A (2015) Complications of Tattoos and Tattoo Removal: Stop and Think Before you ink. J Cutan Aesthet Surg 8:30–36.
45. Colaris MJL, de Boer M, van der Hulst RR, Cohen Tervaert JW (2017) Two hundreds cases of ASIA syndrome following silicone implants: a comparative study of 30 years and a review of current literature. Immunol Res 65:120–128.
46. Ostheimer TA, Burkholder BM, Leung TG, Butler NJ, Dunn JP, Thorne JE (2014) Tattoo-associated uveitis. Am J Ophthalmol 158:637–43.e1.
47. Guimarães LE, Baker B, Perricone C, Shoenfeld Y (2015) Vaccines, adjuvants and autoimmunity. Pharmacol Res 100:190–209.