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Case Report

Kidney Involvement in Asia Syndrome: Case Report of an Uncommon Nephrotic Syndrome

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Abstract

Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) first described in 2011, includes several immune-mediated diseases that are likely to develop in genetically predisposed individuals leading to hyperstimulation of the immune system after their exposure to an adjuvant (vaccine compounds, silicone implant, drugs, infections, metals, etc.). Compared with other clinical manifestations (myalgia, arthralgia, chronic fatigue, neurological manifestations, pyrexia), the description of the renal involvement is very rare. We report a case of nephrotic syndrome in a 37-year-old woman with bilateral silicon breast implant placed in 2017 for cosmetic reason. Kidney biopsy showed acute interstitial tubular nephritis with aspects of membranoproliferative glomerulonephritis. In the months before diagnosis our patient manifested symptoms which oriented for other disease (i.e. Sjogren's, IgG 4 disease, lymphoproliferative issues). Glucocorticoid treatment did not improve while steroids-related side effects appeared. Implant revision was surprisingly found a broken implant, which after its removal and replacement, led to complete remission of the nephrotic syndrome. Compare with other clinical manifestations, renal involvement in ASIA Syndrome is scanty. Our findings may help physicians, such as general practitioners, plastic surgeons and internists, to recognize this pattern of systemic symptoms in women with breast silicone implants and unexplained symptoms.

Keywords: ASIA Syndrome; Breast implant; Nephrotic syndrome

Introduction

ASIA syndrome (adjuvant-induced autoimmune/inflammatory syndrome) was first described in 2011 and defined by major (myalgia,myositis,arthralgia and/or arthritis,chronic fatigue, un-refreshing sleep or sleep disturbances, neurological manifestation, cognitive impairment, memory loss, pyrexia, dry mouth, removal of inciting agent induces improvement, typical biopsy of involved organs) and minor criteria (appearance of autoantibodies or antibodies directed at the suspected adjuvant, other clinical manifestations as irritable bowel syn., specific HLA (i.e. HLA DRB1, HLA DQB1), evolvement of an autoimmune disease), including autoimmunity and systemic symptoms [1]. The placement of silicone breast implants, for cosmetic use, is now a very common practice. Silicone is considered a biologically inert material, in most cases it is well tolerated, but in genetically predisposed individuals it can cause immuno-mediated manifestations, by T cells. Women with breast implant may present a variety of systemic symptoms such as fatigue, chest pain, hair loss, headaches, chills, photosensitivity, chronic pain, muscle weakness, dry eyes, dry mouth, rash, cognitive symptoms, sleep disturbance, anxiety, neurologic issues [2]. The renal involvement in ASIA syndrome is usually very rare, and rarely reported in the scientific literature [3,4]. We report the case of a 37-year-old Cuban woman with silicone breast implants who developed a nephrotic syndrome after the rupture of one of the implants. Kidney biopsy

showed acute interstitial tubular nephritis with associated feature of a membranoproliferative glomerulonephritis.

Case Report

A 37-year-old Cuban woman was admitted to the Padua's University Hospital in December 2021 for headache, dry cough, relapsing fever (body temperature of 38.5 °C) and foamy urine. She was nonsmoker; in her medical history were reported atrial septal defect, asthma bronchitis, tonsillectomy, bilateral silicone breast implants in 2017 after two uncomplicated pregnancies. In November 2019 the patient developed axillary lymphadenopathy associated with axillary pain. For the onset of fatigue and weight loss in January 2020 she was referred for hematologic evaluation. In July 2020, to exclude infection and neoplasm, positron emission tomography (PET) was performed with the evidence of generalized lymphadenopathy (submandibular, cervical, axillary and inguinal). One month later a cervical lymph node biopsy was performed with evidence of follicular and paracortical hyperplasia and plasma-cellular infiltrates IgG4+ (IgG4/IgG >40% with focal distribution), supporting the clinical suspicion for IgG4-related disease. No evident abnormalities in the lymphocyte immunophenotype were found. The patient continued hematologic follow-up for persistence of lymphadenopathy until access to the emergency department in December 2021. At admission, her blood pressure was 117/75 mmHg, heart rate 93 beats/min, O2 saturation 97% in ambient air and fever (37,7°C); physical examination revealed tender cervical, axillary and inguinal palpable lymph nodes; no other manifestations such as edema, rash, xerostomia and xerophthalmia were present. Laboratory findings are shown in Table 1.

	Dec-21
WBC	6,18 x10^9/L
Hb g/l	129 g/L
Platelet count	324 x10^9/L
Serum creatine	65 umol/L
Blood urea	3,72 mmol/L
Electrolytes	Na 138 mmol/L, K 4.1 mmol/L, Cl 104 mmol/L, Ca 2.11 mmol/L, Mg 0.78 mmol/L, P 1.29 mmol/L
Total cholesterol	472 mg/dL
Triglyceride levels	112 mg/dL
TSH	2,46 mIU/L
ESR	120 mm/h
CRP	26 mg/L
24-h proteinuria	11 g/d
Liver function	ALT 13 U/L, AST 23 U/L
Pancreatic function	Amylase 35 U/L, Lipase 15 U/L
Serum protein electrophoresis	Polyclonal hypergammaglobulinemia (21%)
Albumin	11 g/L
ANA	0.486111111
Anti-dsDNA	Negative
ANCA	Negative
Anti-ENA	Negative
Anti-PLA2r	Negative
Complement level	C3 0.93 g/L, C4 0.27 g/L
IL-6 level	5.1 ng/L

Table 1: Laboratory findings at admission in Nephrology Unit.

Infectious diseases (syphilis, toxoplasmosis, tuberculosis, hepatitis B and C, HIV, cytomegalovirus and Epstein Barr virus) and hematological malignancies were excluded. After five days a kidney biopsy was performed. The histopathology of the kidney biopsy showed a well-represented parenchyma composed by 22 glomeruli with expansion of the mesangial matrix and duplication of glomerular basal membrane. An extensive tubular, perivascular and interstitial lymphocytic and plasmacellular IgG4- infiltrate was also detected (Figure 1); immunofluorescence for IgG, IgA

and IgM immunoglobulin was positive with linear/granular staining pattern (Figure 1), and negative for complement cascade fragments C3c, C1q and fibrinogen. The electron microscopy report showed no glomeruli, but confirmed the presence of the infiltrate. To better characterize the severe lymphocytic infiltrate, which was suggestive of a lymphoproliferative disorder, a nested Polymerase Chain Reaction was performed which revealed a proliferation of biallelic monoclonal type B lymphocytes. Taken together these findings were in keeping with a diagnosis of acute tubular interstitial nephritis associated with features of membranoproliferative glomerulonephritis.

Neck ultrasound confirmed the submandibular lymphadenopathy with a patchy parenchyma of submandibular glands. A salivary gland biopsy was performed, showing a lymphocytic and IgG4+ plasmacellular infiltrates, which, however did not support the diagnosis of IgG4-related disease (IgG4/IgG <40%). The patient was treated with corticosteroids (initial dose of 1 mg/kg/day) for several months without an improvement of the nephrotic syndrome but with the onset of steroids-related side effects (insomnia, weight gain, herpes simplex infection, hair loss). After three months, she presented acrocyanosis of hands and feet (Figure 2). A follow-up chest computed tomography (CT) performed in February 2022 showed, in addition to the axillary lymphadenopathy, a thin bilateral peri-breast implants liquid layer. We then asked for a plastic surgical re-evaluation. Implant revision was performed with the surprising finding of a broken implant and the presence of an intracapsular granuloma compatible with periglandular connective tissue associated with lymphoplasmacytic infiltrate making likely that small fragments of silicone had entered into the bloodstream. New breast implants were placed and after twenty days complete remission of the nephrotic syndrome was observed.

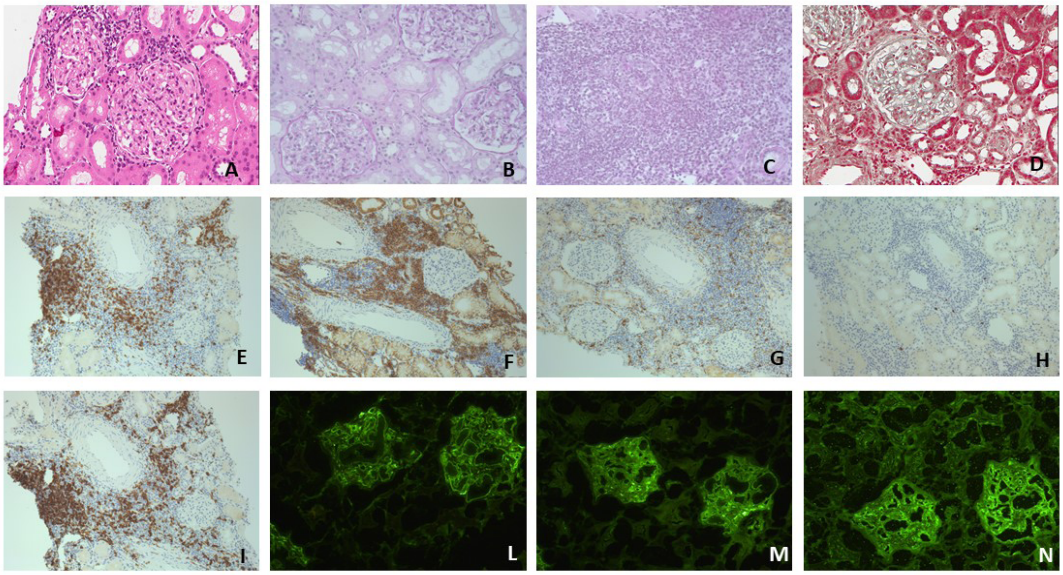

Figure 1: Kidney biopsy findings. Histology and Immunohistochemistry of the severe diffuse inflammatory tubule-interstitial infiltrates and membrano-proliferative involvement of the glomeruli. Glomeruli with expansion of the mesangial matrix, and thickening of the capillary walls, (**A:** HE and **B:** PAS original magnification X20). **C:** inflammatory cells are infiltrating the tubules and the glomeruli (PAS original magnification X20). No relevant fibrosis was presented in the biopsy (**D:** trichrome staining original magnification X20). Immuno-characterization of the inflammatory cells shows: **E:** T lymphocytes (CD3, X10), **F:** Plasmacells (CD138, X10), **G:** macrophages (CD68, X10), **H:** immunoglobulin subclass IgG4 (IgG4 X10), **I:** B lymphocytes (CD20, X10). Immunofluorescence staining: IgM (**L**) with granular peripheral and mesangial staining positivity, original magnification X20. Positivity in granular pattern in the mesangium and parietal capillary wall for IgA (**M**) and IgG (**N**) original magnification x20.

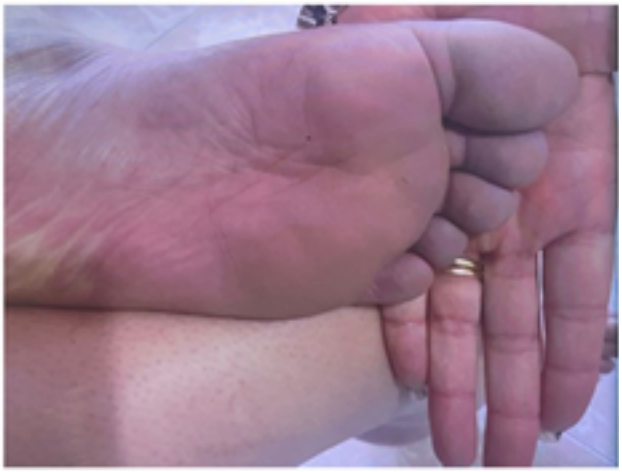

Figure 2: Patient's left feet. Acrocyanosis of all toes.

Discussion and Conclusions

Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) was first described by Shoenfeld et al. in 2011 [1]. It includes several immune-mediated diseases that are likely to develop in genetically predisposed individuals leading to hyperstimulation of the immune system after their exposure to an adjuvant (vaccine compounds, silicone implant, drugs, infections, metals, etc.). These conditions have several aspects in common: the possible appearance of autoantibodies, and the tendency for clinical and biochemical improvement once the causative agent is removed [5]. The diagnostic criteria for ASIA syndrome include major and minor criteria [1].

At least two major criteria, or one major and two minor criteria, are required for the diagnosis of ASIA [6]. Our patient had all four major criteria (silicone breast implants, the presence of typical clinical signs-fatigue, fever- the finding of the inflammatory infiltrate on biopsy of the organs involved, the clinical and biochemical improvement after removal of broken implant) and at least two minor criteria (positive antinuclear antibodies, lymphadenopathy and acrocyanosis), while no information is available regarding genetic background.

Pre-existing allergic disease has been found to be a major risk factor for the development of ASIA syndrome after adjuvant implantation, and our patient had asthma bronchitis [7]. Although symptoms can occur at any time, studies have reported an average duration from 4 to 10 years from breast implantation to the onset of symptoms [2]. Our patient developed the syndrome one year after the prosthesis implantation. Raynaud's phenomenon has been found very often in patients, as shown in various studies [8]: as is the case for our patient who developed acrocyanosis of feet and hands. Compare with other clinical manifestations, renal involvement description in the literature is scanty. Fenoglio R. et al. described in 2018 a case of membranous glomerulonephritis associated with intracapsular rupture of a breast prosthesis. In this case, however, the patient presented with the nephropathy two years after the prosthesis placement, had had a response to steroid treatment, and had presented in the following years relapse (also required some hemodialysis session) but, however responsive to immunosuppressive therapy with improvement of renal function and recovery from hemodialysis [3]. Our patient presented a different histologic picture, characterized by a severe and predominant inflammatory infiltrate in the interstitial tubular compartment and also a glomerular involvement, with the presence of a membranoproliferative glomerulonephritis with immunofluorescence typical for an immune complex glomerulonephritis. In addition, our patient did not respond to steroid treatment. The only successful treatment was the replacement of the broken breast implant, which resulted in a rapid and complete remission of proteinuria after twenty days. This finding might suggest that in our patient, it is not the presence of the prosthesis "per se" that may induce the nephropathy but its rupture with loss of the silicone. Vermeulen and Scholthe reported that rupture was associated with a significant increase in typical clinical manifestation as muscle and joint paint, malaise, unrefreshing sleep, impaired short term memory without mention of renal involvement [9]. Other Authors reported a case of woman with a rapidly progressive new onset diffuse cutaneous systemic sclerosis presenting with scleroderma renal crisis after rupture of silicone breast implants. In this case scleroderma was the first manifestation of ASIA Syndrome followed by renal involvement. This evidence underlining the importance of a link with rheumatologic manifestations and the need for rheumatologic evaluation before silicon breast implant [4].

Another interesting finding in our case report is the histological documentation of a population of monoclonal B lymphocytes at renal biopsy (Figure 1F). Breast implant placement has been indeed also associated with the development of lymphoproliferative pathology, particularly breast implant–associated anaplastic large-cell lymphomas (BIA-ALCL) [10]. For our patient hematologic abnormalities were excluded, however this latter histologic finding will be taken into the due consideration during the follow-up. In the present case report we described an unusual presentation of ASIA syndrome through the finding of nephrotic syndrome. In the months before diagnosis our patient manifested symptoms which oriented for other disease (i.e. Sjogren's, IgG 4 disease, lymphoproliferative issues). In this setting the multidisciplinary approach is important. The lesson we can learn is to also consider renal manifestations as a possible target of ASIA syndrome and monitor at least urine examination in the follow-up of women with breast implantation. Our case adds more information to that already in the literature, compare with other clinical manifestations, renal involvement in ASIA Syndrome is scanty. Our findings may help physicians, such as general practitioners, plastic surgeons and internists, to recognize this pattern of systemic symptoms in women with breast silicone

implants and unexplained symptoms.

References

1. Shoenfeld Y, Agmon-Levin N (2011) 'ASIA' - Autoimmune/Inflammatory Syndrome Induced by Adjuvants. J. Autoimmun 36: 4-8.
2. McGuire P, Clauw DJ, Hammer J, Haws M, Adams WP (2022) Jr A Practical Guide to Managing Patients With Systemic Symptoms and Breast Implants. Aesthet. Surg. J 42: 397-407.
3. Fenoglio R, Cecchi I, Roccatello D (2018) ASIA Syndrome Following Breast Implant Placement. Isr. Med. Assoc. J. IMAJ 20: 714-716.
4. Al Aranji G, White D, Solanki K (2014) Scleroderma Renal Crisis Following Silicone Breast Implant Rupture: A Case Report and Review of the Literature. Clin. Exp. Rheumatol 32: 262-266.
5. Borba V, Malkova A, Basantsova N, Halpert G, Andreoli L, et al. (2020) Classical Examples of the Concept of the ASIA Syndrome. Biomolecules 2020.
6. Maijers MC, de Blok CJM, Niessen FB, van der Veldt AAM, Ritt MJPF, et al. (2013) Women with Silicone Breast Implants and Unexplained Systemic Symptoms: A Descriptive Cohort Study. Neth. J. Med 71: 534-540.
7. Cohen Tervaert JW (2018) Autoinflammatory/Autoimmunity Syndrome Induced by Adjuvants (ASIA; Shoenfeld's Syndrome): A New Flame. Autoimmun. Rev 17: 1259-1264.
8. 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.
9. Vermeulen RCW, Scholte HR (2003) Rupture of Silicone Gel Breast Implants and Symptoms of Pain and Fatigue. J. Rheumatol 30: 2263-2267.
10. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, et al. (2016) The 2016 Revision of the World Health Organization Classification of Lymphoid Neoplasms. Blood 127: 2375-2390.