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ASIA syndrome symptoms induced by gluteal biopolymer injections: Case-series and narrative review

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ABSTRACT

Background: The number of plastic surgery procedures have been rising in the last few years. The morbi-mortality due to illegal use of biopolymers is a public health problem. One of the clinical consequences, foreign body modelling reaction, may be a precursor of ASIA (Autoimmune/Inflammatory disease induced by adjuvants) syndrome.

The objective of this article is to present a case-series study of patients who developed ASIA syndrome following gluteal injection with biopolymers and emphasize the importance of toxic exposure in triggering autoimmune responses. A surgical technique used on some of the patients in the study is described.

Methods: A group of thirteen patients, diagnosed with foreign body modelling reaction, who developed ASIA syndrome confirmed by approved criteria was followed between May 2016 and May 2018. The "Butterfly Wings Technique," a new surgical procedure for patients who have medium to severe compromise, was used on five of them.

A narrative literature review was done to look for subjects with ASIA syndrome and gluteal biopolymer infiltration.

Results: All the patients in the present case-series with foreign body modelling reaction developed ASIA syndrome. Some of them had a background of familial autoimmunity. Five of the patients were surgically treated and saw a clinical improvement after the extraction of the biopolymer with the proposed technique.

The narrative literature review identified 7 articles related to the disease through the database search.

Conclusions: We suggest that foreign body modelling reaction should be considered a precursor to ASIA syndrome. New research projects will be needed in the future to evaluate the factors that determine when ASIA syndrome is triggered in a patient with this reaction.

1. Introduction

Recently there has been an overall 5 % increase in surgical and non-surgical cosmetic procedures. The world leader is the United States with 18.4 % (4,310,180 procedures) while Colombia (South America) ranks sixth in the world with 2.2 % (516,930 procedures) [1,2]. Injectable and resurfacing techniques play an important role in these procedures. Although hyaluronic acid filler is the only FDA approved substance, the use of analog substances from fillers not authorized by the FDA has become popular through the world and produces an impact on the health of those they are used on [3–6]. Different terms have been used to describe the disease caused by allogenic substances that are foreign to the body and injected by doctors or unauthorized personnel, e.g., "foreign modeling agent reactions," "allogenic disease," "Iatrogenic allogenosis," "disease by modeling," or "by biopolymers," "human adjuvant diseases," etc. In general, the materials used are prohibited substances such as industrial oils, silicone, methacrylate, collagen, paraffin, etc. The use of these substances in the short or long-term causes diverse manifestations and complications for those who receive them (Table 1) [7–9]. Some authors think these problems have reached epidemic proportions, especially in Latin-America [10–14].

It has been shown, through some in vitro studies, the deleterious

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Table 1
Diverse complications by filler type.

Filler Type	Clinical Complications [a]	In vitro deleterious effects
Calcium hydroxylapatite (caHA)	Infection, pain, swelling, necrosis, arterial embolization, nodule, blindness [b], blanching [c] [27,28,29,30]	• Increases in the secretion of TNF-α, IL-1, IL-8, IL-10 and proMMP-2 and -9 and decreases in the secretion of IL-6 in Monocytes culture exposed to caHA [i] [15]
Collagen	Discoloration, blindness [b], maldistribution, infection, skin necrosis, granuloma formation, foreign body reactions [29,31]	• Collagen coated with PLLA was phagocyted by one in vitro cell line and TNF-α was released in cultured cells. [16]
Hyaluronic acid	Swelling, infection, nodule, pain, arterial embolization, bleeding, blindness [b], blanching [c], Tyndall effect [d] [27,28,29,30,32]	• Hyaluronic acid supported the growth of bacterial biofilm in vitro. Multiple needle passes through a biofilm-contaminated surface resulted in significantly increased contamination of filler material [j] • In a murine in vitro culture system,135 KDa fragments of the hyaluronan induced dendritic cell maturation and initiated alloimmunity acting as an innate immune agonist • In an in vitro analysis, three cellular lines (two keratinocyte cell lines, and one human dermal fibroblast) were cultured and exposed to hyaluronic acid cross-linked with 1,4-BDDE or with PEG. PEG-treated cells showed markedly lower cytotoxicity, ROS production, and inflammatory responses than BDDE-treated cells. [17,18,19]
Liquid silicone (oil)[e]	Allergies, blindness [b], inflammatory reactions, migration, granulomatous reactions, rejection, Silicone embolism syndrome, ulcers, Skin dyschromia, infections [29,33,34]	• Silicone microparticles were phagocyted by one in vitro cell line • Immuno-reactivity to medical-grade silicone dermal filler was evaluated in vitro in PBMC. Silicone induced a release of proinflammatory cytokines but does not acted as a polyclonal activator of CD4 + T cells. [16,20]
Paraffin	Blindness [b], inflammation, infection, embolism, yellowish skin plaques, granulomatous foreign-body reaction (paraffinoma), fistulization, migration, scarring [29,35]	
Polyacrylamide hydrogel [f]	Allergic reaction, blindness [b], hypersensitivity reactions, migration, contour abnormalities, abnormal skin sensation, pain, induration, malignant breast tumors, aseptic inflammation, leakage, hematoma. [29,36,37]	• Growth of bacterial biofilm in vitro [j] [17]
Poly-L-lactic acid (PLLA)	Nodule, granuloma, infection, pain, swelling, bleeding, blindness [b], paresthesia [27,28,29,38]	• Growth of bacterial biofilm in vitro j • Cultures exposed to PLLA exhibited a reduction in both cell proliferation and viability compared to control in all time points Histologic analysis showed the presence of multinucleated cells • HAEC were treated with different volume percentages of extract of pre-degraded PLLA in vitro, and the cell growth curve and morphological changes were examined. The extract of PLLA caused significant growth inhibition and release of NF-κB, VEGF and VCAM-1 in HAEC with volume percentage-dependence. [17,21]
Polymethylmethacrylate [g] (PMMA)	Nodule, localized foreign body reaction, anaphylaxis, blindness [b], Infection, biofilm [h] [28,29,32]	• Three in vitro different cell lines could phagocytose polymethylmethacrylate microspheres (<20um). • In vitro studies reveal that macrophages rapidly released arachidonic acid and derived inflammatory mediators in response to PMMA particles. However, cells exposed to PMMA are lethally damaged, as reflected by the subsequent leakage of their intracellular LDH. [16,22]

a: Most of them from case report, case series, regulatory agencies databases or medical malpractice litigation databases. Majority of the reports injected in facial area. All of them can produce minor or transient effects such as edema, erythema, mild pain and ecchymosis. b: Facial injection and vascular complications, c: Pallor or blanching phase secondary to intra-arterial injection, d: bluish hue that is visible within the skin caused by too superficial placement of dermal filler, e: prohibited by the regulatory agencies due to the evidence of severe side effects, f: Mainly reported in breast augmentation with polyacrylamide hydrogel injections, g: microspheres frequently suspended in a water-based carrier gel composed of bovine collagen, h: most frequent with permanent fillers, i: This was evaluated by using nanoporous hydroxyapatite powders synthesized by hard or soft templating, but not by using other presentations, j: Similar results were shown for polyacrylamide gel, and poly-L-lactic acid. BDDE: Butanediol diglycidyl ether; caHA: Calcium hydroxylapatite; CD4 + T:T lymphocyte (helper); HAEC: Human aortic endothelial cells; IL-1: Interleukin1; IL-10:Interleukin 10; IL-8:Interleukin 8; Kda: Kilodaltons (molecular weight); LDH: Lactate dehydrogenase; NF-κB: Nuclear factor kappa beta; PBMC: Peripheral blood mononuclear cells; PEG: Polyethylene glycol; PLLA: Poly-L-lactic acid; proMMP: Prometalloproteinase; ROS: Reactive Oxygen Species; TNF-α:Tumor Necrosis Factor alpha; VCAM-1:Vascular cell adhesion molecule 1; VEGF: Vascular endothelial growth factor.

effect on cell proliferation, cell viability, cytotoxicity effect, inflammatory responses, and expression of inflammatory cytokines in treated cells (see Table 1) [15–22]. However, some in vitro studies have shown the absence of those effects, particularly in those that evaluated hyaluronic acid based dermal filler [21,23], hyaluronic acid cross-linked with polyethylene glycol [24] or hydroxyapatite spherical particles cross-linked with sodium hyaluronate [25] as well as calcium hydroxylapatite microspheres [26].

At this point, it is important to highlight that biopolymers are recently used in medical areas apart from cosmetic applications, such as cancer imaging identification and oncological therapies [27]. Radu et al. [28] developed in vitro studies using Poly 3-hydroxybutyrate-co-3-hydroxyvalerate as targeted anti colorectal cancer nanocarrier (bio--nanocarrier) loaded with 5-fluorouracil; the research suggested low cytotoxicity and it resulted efficiently to kill adenocarcinoma cells. In addition, Taghizadehghalehjoughi et al. [29] developed an in vitro and in vivo animal model with hydrochloride -loaded poly-lactic-co-glycolic acid nanoparticles for the treatment of glioblastoma multiforme, the findings were promising due to the results related to significant volume reduction of the extracted tumor. On the other hand, biopolymers are under research in diverse fields of medicine, such as biopolymeric films as delivery vehicles for controlled release of medications to treat chronic skin diseases [30]; natural and synthetic polymer nanocomposites in bone tissue regeneration [31]; 3D-printed biopolymeric encapsulation system for the transplantation of endocrine cells [32]; structured medical hemostatic sponges as a medical devices for stop bleeding and for close the wound [33]; nanodrug carrier for treating rheumatoid arthritis [34]; biopolymer-based scaffolds for corneal stromal regeneration [35]. These are some examples of potential biopolymers applications, however, through this review, we will focus on plastic surgery uses.

The body areas, in cosmetic procedures, where the unknown materials are most frequently injected are buttocks (8–72 %) and breasts (12–16 %) [10,36,37]. This causes local complications such as ulcers, livedo reticularis, nodules, etc. The gluteal area is of specific interest because the musculature of this region controls the movements of the hip, and supports the back and the iliotibial tract [38,39]. Therefore, a sitting position will generate more pressure and worsen symptoms. It is also the area that suffers trauma when patients self-medicate with intramuscular medications. What is also well-known is that the migration of foreign materials to the lower back is a frequent complication when they are infiltrated subcutaneously. Likewise, when the infiltration is deep, the material migrates to the lower inguinal region, perineum, and lower limbs. It also enters and moves through the endolymphatic tract [7,36,37].

At the systemic level, the patient may develop polyarthralgia, myalgias, and cognitive and sleep disorders. These manifestations have been observed in 60 % of the patients who have the autoimmune/inflammatory syndrome induced by adjuvants (ASIA) [40,41]. This disease consists of an antigen-specific response to an adjuvant substance due to its ability to produce widespread activation of various immune cells and inflammatory pathways [40,42]. As a result, the innate and adaptive immune response is activated which then increases the local and systemic reaction to antigens by the release of chemokines and cytokines which, in susceptible individuals, may ultimately lead to the development of autoimmune diseases [43]. Biopolymers have been recognized as adjuvants triggering ASIA syndrome since they are part of the “autoimmune ecology” (i.e. complex interactions between individuals and their environment and the associated mechanisms that lead to a breakdown in immune tolerance and, therefore, to the development of autoimmune diseases) [44,45]. The scientific academy has accepted the clinical criteria that Shoenfeld’s et al. recommended for ASIA Syndrome [40,46].

The therapeutic approach to this type of pathology is complex because of the diverse anatomical areas in which the modeling material is infiltrated, and the different techniques used. In fact, the approach will differ based on the depth at which the material is placed. Various types of surgical treatments have been proposed. Also, in cases where surgery cannot be done or the symptoms are persistent, medical treatment is used [47,48].

Our hypothesis is that foreign body modelling reaction could be considered a precursor to ASIA syndrome. The purpose of this study is 1) to describe a group of patients who received an injection of biopolymers in the gluteal area and then developed ASIA syndrome, 2) to evaluate a possible relationship between exposure to risk factors and ASIA syndrome, and 3) to describe a surgical technique used on some of the patients in the study.

2. Patients and methods

First-time consecutive subjects who attended to the plastic surgery department with clinical manifestations of foreign body modelling reaction between May 2016 and December 2016 after the injection of biopolymers or unknown substances in the gluteal region were enrolled in this case-series. These patients were evaluated and followed until 2018 in a search for ASIA syndrome or immunological diseases based on international criteria [ACR/EULAR guidelines for systemic lupus erythematosus (2019), rheumatoid arthritis (2010), and Sjögren’s syndrome (2016) respectively]. Disease definition, inclusion, and exclusion criteria are shown in Table 2.

2.1. Study protocol

A case-series study was done. The chronological assessment was as follows (Table 2): 1) Baseline: detailed clinical evaluation and verification of fulfillment of inclusion and exclusion criteria; 2) Follow-up visits every three months (the completed clinical evaluation [49–53] was repeated every three months as shown in Table 2); 3) Diagnostic images were taken and laboratory tests were done at baseline and repeated annually. Clinical evaluation, laboratory tests, and imaging examination are shown in Table 2.

Furthermore, a narrative literature review was carried out (*supplementary material 1)*.

2.2. Surgical Technique (“Butterfly Wings”)

This procedure is suggested for patients who meet at least one of these criteria: active migration of the biopolymer, distortion or significant functional disturbance, presence of cutaneous ulcerations, fistulous trajectory or recurrent infections, and development of an inflammatory or autoimmune disorder associated with the infiltration of these substances.

The surgical technique (developed by Dr. Montealegre G) is based on the same procedures used for the management of post-bariatric patients. This requires the resection of the excess skin after the patient has lost massive weight. Preoperative markings are drawn in the standing position. They consist of sketching a design in the medial area near the intergluteal cleft without exceeding the upper limit of this cleft and without going below the infragluteal fold. Under general anesthesia, the patient is placed in a prone position. Incisions are made along the demarcated lines. Then, the cellular subcutaneous tissue is dissected to the *gluteus major* muscle fascia at the inner edge adjacent to intergluteal fold. The adipo-dermal flap, including the de-epithelizated area with a thickness of 2 cms from medial to lateral, is elevated. After that, a bloc resection of the allogenic substance from the subcutaneous to supra-fascial layers of the *gluteus major* muscle is done. Next, four de-epithelized medial flaps are cut and each is folded over on itself, Then, moving clockwise 1-3-4-6 on the right buttock and 11-9-8-6 on the left buttock in order to maintain the gluteal contour, each flap is fixed separately to the muscular fascia with polyglactin 1-0. The incision is closed by layers (fat and dermal) with polyglactin. A negative pressure system is left and fixed with 2-0 silk. Skin wounds are closed by intradermic suture with polypropylene (Fig. 1).

Table 2
Disease definition, Inclusion and exclusion criteria and clinical and laboratory evaluation.

Disease definition	Foreign body modelling reaction (i.e. Iatrogenic Alogenosis) Diagnosis One of the following • Local manifestations: edema, angioedema, skin induration, plaques, panniculitis, swelling/ tender nodules (with or without fistulization or discharge of sterile pus or filler material), non-infectious adverse reactions related to filler injection OR • Systemic reactions: fever, arthralgia, arthritis, myalgia, muscle weakness, chronic fatigue, generalized aches, distant skin lesions, xerophthalmia, xerostomia [7,9]. Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) Diagnosis All patients underwent a complete evaluation to see if they fulfilled the criteria as by criteria: • Defined by Shoenfeld's et al [19]
Inclusion criteria	First time consultation patients with clinical manifestations (local or systemic) of foreign body modelling reaction were included. From this group, those with a biopolymer injection in the gluteal region with or without a previous history of surgical removal of the material were chosen.
Exclusion criteria	• Patients with an established diagnosis of autoimmune disease (Systemic Lupus Erythematosus, Rheumatoid Arthritis, Sjogren's syndrome) according to ACR/EULAR guidelines 2019, 2010, 2016 respectively for each autoimmune disease. • Previous thyroid disease. • Previous neoplastic disease before the exposure to allogenic substances or at the moment of the medical consultation (If it was not possible to establish the temporal relationship between the application of the allogenic substance and the disease).
Clinical Evaluation (At baseline and every three months)	• Detailed clinical record of demographic data, present or previous comorbidities and familial background (including familial autoimmunity [28] toxic exposure, obstetric outcomes, and other comorbidities. • Complete rheumatological examination searching for autoimmune diseases (by a rheumatologist) based on fulfilled standard validated criteria (baseline for exclusion criteria and follow up). • Muscular strength evaluation (MRC) [29] • Unstimulated Whole Salivary Flow [30] • Fatigue based on the Functional Assessment of Chronic Illness Therapy (FACIT) [31] (those positive were evaluated using the Spanish version of the Fatigue Severity Scale) [33].
Biopolymer injection characteristics	• Date of polymer infiltration. • Type and volume of the injected substance. • Area of infiltration. • Latency time with Foreign body modelling reaction were reported.
Laboratory and Imaging examination	Standard blood samples were collected for the following measurements (All of these tests were repeated every year during follow-up): • Acute-phase reactants: C-Reactive Protein (CRP), and erythrocyte sedimentation rate (ESR) • Liver function (Glutamic Oxaloacetic Transaminase (GOT)), and Glutamic Pyruvic Transaminase (GPT) • Immunological profile: immunoglobulin levels (IgG-IgM)), Antinuclear Antibodies (ANAs), Antineutrophil Cytoplasmic Antibodies (ANCAs), Rheumatoid Factor (RF), Thyroid Stimulating Hormone (TSH), Free Thyroxine (T4), Antithyroglobulin Antibody Test, and Thyroid Peroxidase Antibody test (TPO). • Magnetic Resonance Images (MRI) of the primary filled areas were taken. • Biopsies of buttock lesions were taken when the patients underwent surgical removal of biopolymers.

2.3. Statistical analysis

All the information collected was organized in codified clinical registries. A database was created using Microsoft Excel software ® (v. 2013), and absolute and relative frequencies as well as measurements of central tendency and dispersion were calculated.

3. Results

3.1. Patient results

Of a total of 5014 patients (Fig. 2) who came during the observation period, 66 had biopolymer gluteal infiltration, only 13 met the inclusion criteria (Table 2) of "first-time clinic visit" while the remaining 53 who came only for follow up visits were excluded. All of the 13 subjects had received biopolymer injections in the buttocks and agreed to sign the consent form. Two of them did not complete the 2 years of follow up and decided to not provide more information about their clinical history. One patient died during follow up. In the end, the completed study included ten (n = 10) patients.

Aesthetic procedures had been done on all of them in "clandestine clinics" by staff whose training is unknown. Eleven subjects were women, and 2 were men with gender dysphoria. Mean age was 38.3 years old (SD 8.48). Most of the patients were injected with unknown substances. Three received injections of known substances. Two of the 3 received injections of mineral oil and 1 of Biogel. All of them developed local manifestations of foreign body modelling reaction (Table 2).

The average time between the infiltration of the substance and clinical manifestations of foreign body modelling reaction was 27.8 months (SD 8.48). More than 50 % of the patients had familial autoimmunity and some of them had been exposed to other toxics (Table 3) and 7 patients had had additional aesthetic procedures done. There were no differences in the presentation of the clinical manifestations between those patients who had previous aesthetic procedures and those who did not. During follow-up, 3 patients developed hypothyroidism, one of which had elevated anti-thyroglobulin antibodies. None were positive for other autoantibodies. One patient had elevated IgG/IgM (the other five patients who were evaluated had normal levels). Furthermore, 9 patients (out of 12) had an elevated ESR at the last follow up appointment while 2 who had had an elevated ESR at the beginning returned to a normal level. In the case of CRP, 13 had normal levels at the beginning, and the 12 remaining in the study had normal levels at the end. Liver function was elevated in three patients for the first year with normalization during follow-up. Nine patients used oral contraceptive methods. One patient had an alteration in unstimulated whole salivary flow. One woman had 4/5 strength in her lower limbs. Mean FACIT (Table 3) score was 40.6 (SD 9.6). Three patients had significant fatigue (FACIT and high score in the Fatigue Severity Scale).

Regarding ASIA diagnosis, eleven patients met Shoenfeld's criteria for ASIA syndrome (Table 4), but three patients were incompletely evaluated for clinical symptoms of ASIA (patients 10, 11 and 13) and four had a very low clinical ASIA score (patients 2,3, 7 and 12).

3.2. Surgical procedures

Biopolymers were removed in the case of 7 patients and 5 of them had a partial improvement (Table 3). One patient had a background of Human Immunodeficiency Virus without adherence to medical

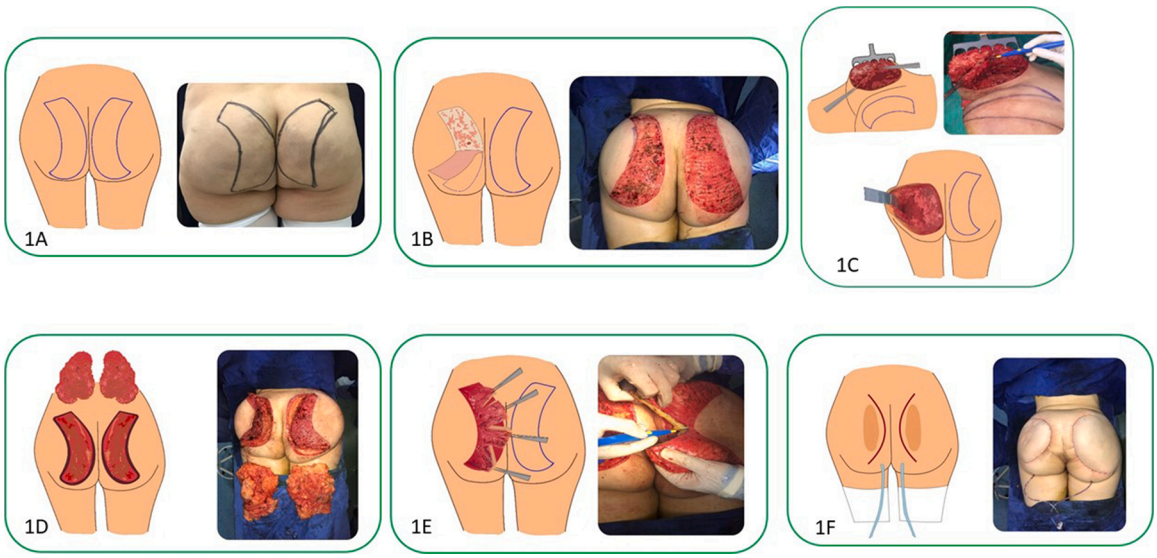

Fig. 1. Butterfly Wings Design technique.
a. Preoperative markings are done in the standing position. **b.** De-epithelization of the flap. **c.** The cellular subcutaneous tissue is dissected to the *gluteus major* muscle fascia, subcutaneous tissue elevated to find biopolymers **d.** Bloc resection of biopolymer. **e.** Four de-epithelized medial flaps are cut, and each is folded over on itself. Then, they are fixed separately to the muscular fascia. **f.** Closed by layers (fat and derma) with polyglactin and a negative pressure system is left and fixed.

treatment. The patient was admitted with a critical complication (necrotizing fasciitis). Therefore, a partial biopolymer removal by surgical debridement and washout was done, but the patient died due to sepsis after procedure. The period needed to see a clinical improvement in the whole group after biopolymer resection was approximately one to two months.

The surgical "Butterfly Wing Technique," was used on 5 patients (Fig. 3) all of whom experienced clinical improvement. A histopathological study was carried out on samples obtained in surgery from 3 patients. The biopsies showed granulomatous chronic inflammation with foreign body reaction, mature adipose tissue with histiocytes, and vacuoles with seal ring cells associated with fat necrosis and allogenosis without malignancy.

Results from the narrative literature review are shown in *supplementary material 1*.

4. Discussion

ASIA syndrome is a recently identified condition related to exposure to adjuvants. This is a report on thirteen patients who developed foreign body modelling reaction after exposure to biopolymers in the buttock area and whose were followed for two years due to a possible relationship between this reaction and the development of ASIA syndrome which is supported by a narrative literature review.

Nowadays, the concept of beauty is related to pre-established social paradigms or socially transformed stereotypes based on the era and culture [54,55]. In fact, there have been several efforts to define it such as attempting to isolate the various phenotypical [i.e., physical] proportions underlying beauty (i.e. waist to hip ratio curvaceousness or the degree of "hourglass shape," etc.). Therefore, many people focus their attention on the fat located on the buttocks in particular, and this influences some individuals to use fillers in that area [56]. According to recent statistics, there were 20,673 buttock augmentation procedures in the US in 2016 [2]. In Colombia, information is not complete due to a lack of registration. There are a number of unauthorized and "clandestine" sites with personnel whose training is unknown where these types of procedures are done, and fillers that have not been approved by regulatory agencies are used. This is, therefore, a public health problem because patients put their health and life at risk [57,58].

Herein thirteen patients are described (two of them did not complete the 2 years of follow up and one died during follow up) with gluteal biopolymer exposure and foreign body modelling reaction, and who developed ASIA syndrome as a result. However, when this information is contrasted with the narrative literature review, few cases were found where there was exposure to gluteal biopolymer and development of ASIA syndrome. The cases found are described in supplementary material 1.

The general course of foreign body modelling reaction is quite variable. The spectrum of manifestations fluctuates from mild to severe depending on the amount of substance infiltrated, the area of application, and the length of exposure as well as other variables (Table 1) [59–70]. The initial manifestations usually correspond to a local inflammatory process characterized by pain and continuous or intermittent hyperemia that lasts several months or years after the application of the modeling substance. Subsequently, the migration of the substance to peripheral or distal areas takes place with similar manifestations, progressive local and distant hyperpigmentation, development of a collateral venous network, cutaneous atrophy, and the formation of ulcers. Depending on the depth of the infiltration, the substance may be deposited on the fascia thus affecting the skin with an additional compromise of subcutaneous cellular tissue and the underlying muscles. A high percentage of patients with foreign body induced ASIA may develop autoimmune diseases as shown by Cohen Tervaert, et al. [71] where 50 percent of patients suffering from silicone implant incompatibility syndrome and associated ASIA syndrome developed a systemic autoimmune disease. In addition, Watad et al. [72] found that, compared with women without foreign body modelling agents, the risk of developing an autoimmune disease increased 45 %. In the present case-series, all patients presented at least one local manifestation of foreign body modelling reaction prior to developing ASIA syndrome.

Shoenfeld and Agmon-Levin described ASIA syndrome [40,73] in 2011. Several of the mechanisms in the pathological pathways of ASIA syndrome include genetic factors [37,47], innate immune dysregulation, release of inflammatory cytokines, T cell impairment, altered balance between Th1 and Th2 immune response with an excessive Th1 immune response, specific antigen-driven local immune response through activated Th17 cells, B cell activation, epigenetic modifications, etc. [43,44].

Taking the chain-of-events relationship between foreign body modelling reaction and ASIA syndrome in the case series, it is our

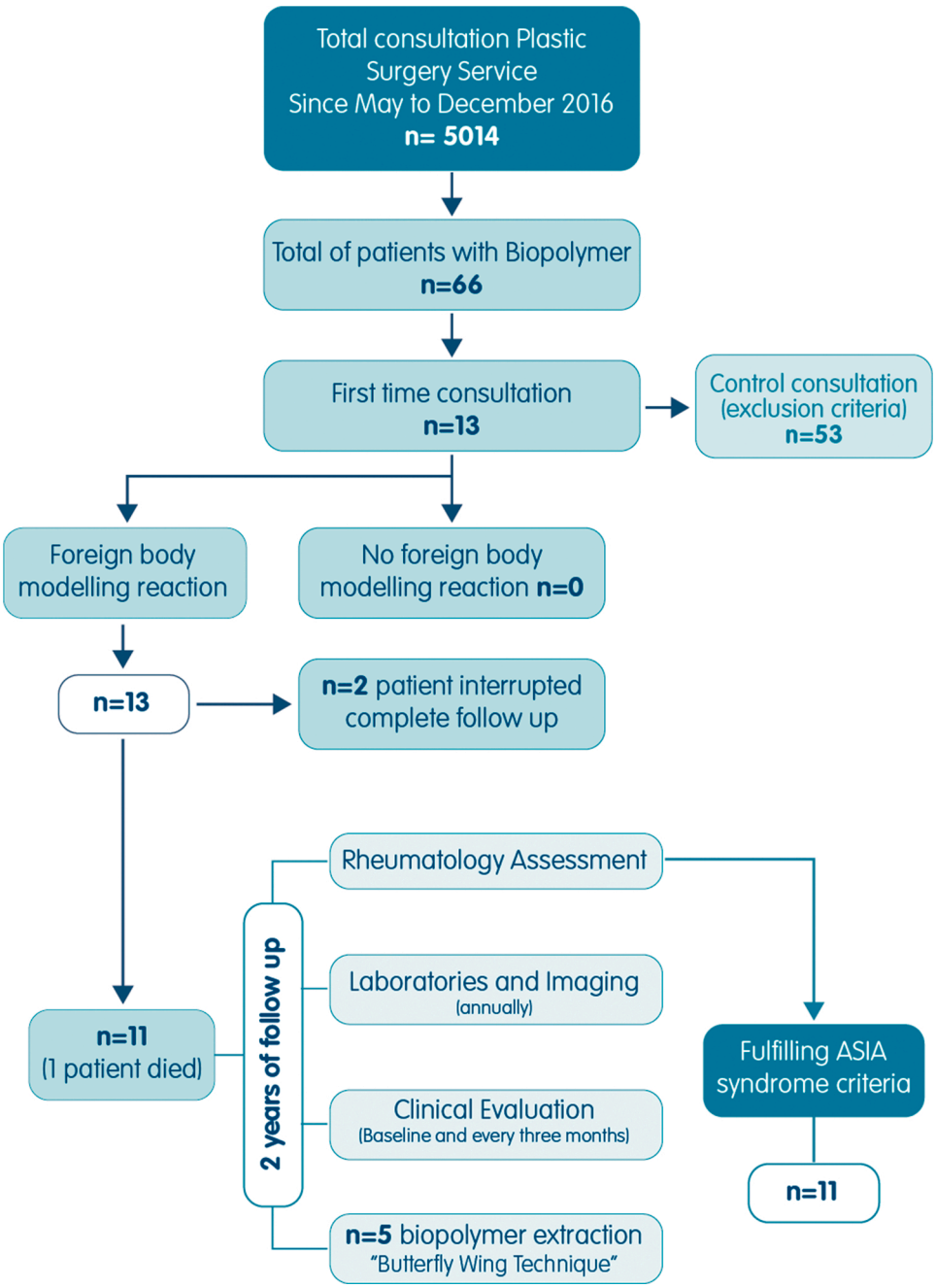

Fig. 2. Flow chart of the study cohort at baseline and at follow-up.

suggestion that this reaction could be considered part of the spectrum of the disease, possibly one of the first steps between the biopolymer injection and later development of ASIA syndrome. González et al. [74] demonstrated the variable, multiorganic, toxic, immunological, progressive, and fatal outcomes that are triggered following the infiltration of some substances by means of an animal model which reproduced pathological effects following infiltration of the substances commonly causing foreign body modelling reaction.

The subjects in the present study were found to have a significant familial autoimmunity background. This, therefore, supports the hypothesis of a predisposed, genetically susceptible host, [i.e. familial autoimmunity or familial autoimmune disease history] who receives two or more different stimuli, and then develops an adaptive and innate immune response alteration which increases the risk of an abnormal clinical response. A total exposure effect on individuals with a genetic predisposition can be hypothesized. An explanatory case from the cohort in this study is shown in *Supplementary material 2*. This case shows a possible total exposure effect leading to ASIA syndrome with exposure to toxics such as cigarettes, tattoos and hair dyes prior to biopolymer infiltration. Therefore, the importance of a comprehensive clinical evaluation is highlighted (familial autoimmunity, pre-existing autoimmune phenomena, and previous exposure to toxics) thus balancing the individual risk/benefit of using prosthesis or dermal fillers for aesthetic purposes [36,37,44,75–78]. Some authors agree that both a pre-existing immunologic disease and a genetic predisposition have been found to be important risk factors for the development of ASIA syndrome [46,79]. In contrast, information associated with exposure to tattoos, cigarette or alcohol consumption, hair dyes or piercings before or after a filler injection that would explain the development of ASIA was not found through the narrative literature review *(Supplementary material 1)*.

Table 3
Clinical characteristics of patients, biopolymer extraction, surgical procedures and clinical results.

	Age (Years)	Gender	Familial AID	Personal AID	Has the material been removed?/ Did the removal induce clinical improvement?	Other cosmetic procedures/ toxic exposure	UWSF	Muscular strength (MRC) Superior/ inferior limbs	FACIT	FSS
1	34	Female	SS[c]	Thyroid disease in pregnancy[j]	No/NA	Mammoplasty augmentation and liposuction/ Tattoo and hair dyes	N	5/4	25	46
2	44	Female	SS[c]	N	Yes[k]/Yes	Mammoplasty augmentation and liposuction/ Tattoo and hair dyes	N	5/5	47	9
3	37	Female	N	N	Yes[k]/Yes	N/ Hair dyes	N	5/5	46	9
4	35	Female	N	Subclinic hypothyroidism[j]	Yes[l]/No	Liposuction and lipectomy/ Tattoo, hair dyes and muriatic acid	N	5/5	30	59
5	52	Female	Psoriasis[d]	N	No/No	N/ Tattoo and hair dyes	P	5/5	48	16
6	45	Female	Reumathoid arthritis[e], Hyperthyroidism[f]	N	Yes[k,l]/ Yes	Mammoplasty augmentation and liposuction/ Tattoo Hair Dyes	N	5/5	31	36
7	40	Female	Diabetes type 1[g]	N	No/NA	N/ Hair dyes and piercing	N	5/5	41	10
8	25	Female	Antiphospholipid syndrome[e], psoriasis[h], vitiligo[i]	N	Yes[k]/Yes	NA/ Tattoo	N	5/5	38	37
9	46	Female	Hypothyroidism[e,f]	Hypothyroidism[j]	Yes[k,l]/Yes	Lipectomy/ Tattoo and hair dyes	N	5/5	50	9
10[a]	40	Male	N	N	Yes[m]/No	NA	NA	NA	NA	NA
11[b]	31	Female	NA	NA	No/NA	Mammoplasty augmentation and lipectomy	NA	NA	NA	NA
12	31	Male	N	N	No/NA	Sex reassignment[j], mammoplasty augmentation[j], facial feminization surgery[j], rhinoplasty[j]/ Hair dyes	N	5/5	50	9
13[b]	39	Female	NA	NA	No/NA	NA	NA	NA	NA	NA

AID: Autoimmune disease, SS: Sjögren's Syndrome, FACIT: Functional Assessment of Chronic Illness Therapy (Higher score indicates better quality of life), FSS: Fatigue severity scale, MRC: Medical Research Council, N: Negative, NA: Not Available, P: Positive, UWSF: Unstimulated Whole Salivary Flow Rate (positive if≤1,5 mL/15 min).
a: Death, b: Lost follow up, c: Aunt, d: Son, e: Mother, f: Sister, g: Niece, h: Cousin, i: Uncle, j: After biopolymer injection, k: Butterfly Wings Technique, l: Assisted Liposuction (Extrainstitutional), m: Surgical debridement and washout.

Based on the toxic effects that these dermal fillers generated in the quality of life of the patients, several surgical techniques have been proposed which include extensive surgical resection and subsequent reconstruction using local or microsurgical flaps, particularly when the disease affects the mammary and facial areas [80,81]. There is no standard treatment for gluteal complications from injections of foreign materials [37] and, in addition, the scientific literature is scarce. Gordillo-Hernández et al. [8] retrospectively describe a cohort of 128 patients with human modeling disease, of which 86 cases involved the gluteal region. Although they do not report the exact number of those for whom the material was extracted, they highlighted the use of surgical procedures when medical treatment has failed. They showed that the procedure requires very extensive resections since the substances generally affect the whole anatomical region involved and are widely scattered. Furthermore, the resection causes significant skin covering defects, which require grafts or flaps of various sizes and generally result in poor and disappointing aesthetic results for patient and surgeons. Martinez Villarreal et al. [10] describe a retrospective case series of 23 patients with foreign modeling agent reaction, 38.5 % in buttocks all of whom had several skin changes such as sclerosis and ulceration as well as systemic complications. Only in the case of 11 patients did they describe a treatment that generally consisted of standard wound technique healing and diverse debridement modalities including surgical debridement with removal of infiltrated areas and reconstructive procedures. They highlighted the fact that surgical removal can be difficult given that large amounts of injected modeling agent tend to mix with healthy tissue. Other techniques mentioned included conventional liposuction, ultrasound assisted liposuction and bloc removal of modeling agents [82].

There is limited and conflicting information regarding the treatment. In some cases, it is necessary to remove the unknown injected substance because of the risk of infection, scarring, severe granulomatous or inflammatory reaction with significant fibrosis. In addition, there is a lack of information about the criteria for removing the material based on ASIA criteria. This should be considered for upcoming research. That is why our research group proposed a new surgical technique called the "Butterfly Wing Technique." The proposed technique allows a bloc extraction of the exogenous substance with marked improvement in local and systemic symptoms and quality of life. Also, this technique gives good aesthetic results. There was a clinical improvement for all our patients after surgery. There are some complications with our technique such as late seroma. However, approximately 80 % of the procedure is done by means of a biopolymer bloc removal, the harmony of the gluteal area is maintained, and the surgical wound can be hidden by the underwear. Most patients see an improvement in the local and systemic symptoms as well as in their quality of life.

To draw the conclusion that the extraction of biopolymers may be done on asymptomatic patients with a history of immunological disease is not justified. Instead, the patient's risk criteria must be considered.

Some patients with foreign body modelling reaction have been treated with colchicine for the granulomatous reaction to foreign bodies in response to the injection of exogenous oily substances [mineral,

Table 4
Shoenfeld's criteria for ASIA syndrome.

Patients	Major criteria									Minor Criteria			ASIA Diagnosis
		"Typical" clinical manifestations											
	Exposure to an external stimuli (Infection, vaccine, silicone) prior to clinical manifestations	Myalgia, myositis or muscle weakness	Arthralgia and/or Arthritis	Chronic fatigue, unrefreshing sleep or sleep disturbances	Neurological manifestations (especially associated with demyelination)	Cognitive impairment, memory loss	Pyrexia, dry mouth	Removal of inciting agent induces improvement	Typical biopsy of involved organs	The appearance of autoantibodies directed at the suspected adjuvant	Other clinical manifestations (Eg. Irritable Bowel Syndrome)	Evolvement into an autoimmune disease (i.e. MS, SSc)	
1	p	p	p	p	n	p	n	n	na	n		Subclinical Hypothyroidism	p
2	p	n	p	n	n	p	n	p	p	n	Iron deficiency anemia, Bronchitis	n	p
3	p	n	p	n	n	n	n	p	na	n	Carpal tunnel syndrome	n	p
4	p	p	p	p	n	p	p	n	na	n	Depression, gastroesophageal reflux	Subclinical Hypothyroidism	p
5	p	p	p	p	n	p	p	na	na	n	Gastric ulcer, hemorrhoids, facial palsy, blepharospasm, depression, bradycardia	n	p
6	p	n	n	p	n	n	p	p	na	n	Neurocardiogenic syncope	n	p
7	p	n	n	p	n	n	n	na	na	na	Migraine, gastritis, gastroesophageal reflux disease, recurrent bacterial vaginosis	n	p
8	p	p	p	p	n	n	n	p	p	n	Gastritis, irritable bowel syndrome, recurrent Urinary tract Infection	n	p
9	p	n	p	p	n	p	p	p	p	n	n	Hypothyroidism	p
10[a]	p	p	p	p	na	na	na	n	p	n	n	n	p
11[b]	p	na	na	na	na	na	na	na	na	na	na	na	na
12	p	n	p	n	n	n	n	na	na	n	n	n	p
13[b]	p	na	na	na	na	na	na	na	na	na	na	na	na

Patients recruited in the study for following. The diagnosis of the disease is made with 2 major criteria or 1 major plus 2 minor criteria. a: This patient died, during follow up, b: Lost follow up.
MS: Multiple Sclerosis, n: Negative, na: Not Available. p: Positive, SSc: Systemic Sclerosis. Table taken and adapted from: Shoenfeld Y, Agmon-Levin N. "ASIA" - Autoimmune/inflammatory syndrome induced by adjuvants. J Autoimmun [Internet]. 2011;36(1):4–8.
Available from: https://doi.org/10.1016/j.jaut.2010.07.003.

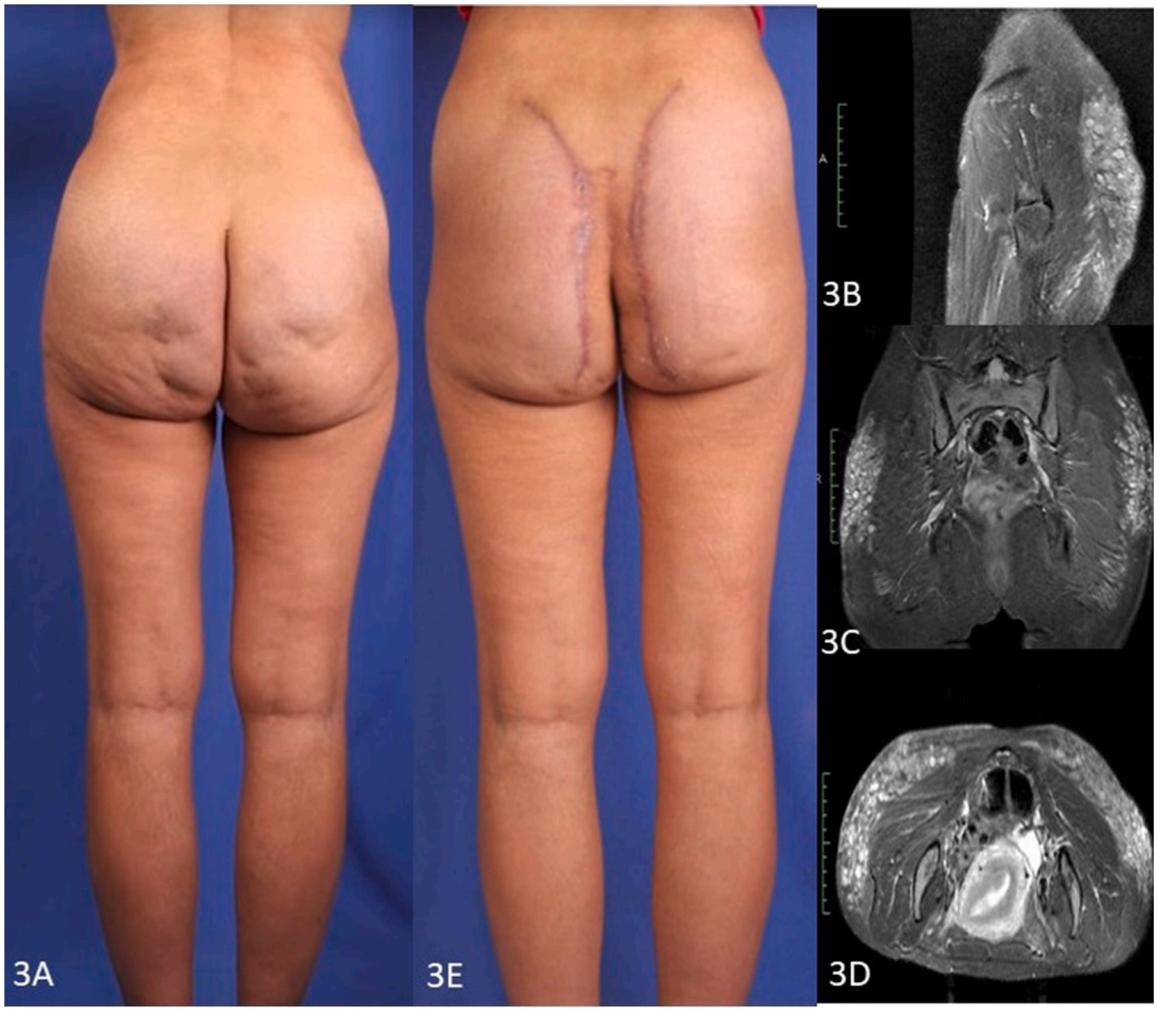

Fig. 3. The images correspond to patient number 2. Clinical case of woman with biopolymer injection, Magnetic Resonance Image (MRI) findings, and results after surgery.
a. Pre-surgical photograph of a 45-year-old woman with a 10-year history. Infiltration of an unknown substance at the level of the buttocks. Changes at the skin level such as hyperpigmentation, nodules, and irregularities are observed. **b.** Axial plane of MRI **c.** The sagittal plane of MRI **d.** The coronal plane of MRI. On the three images, a diffuse alteration in the signal intensity of subcutaneous cellular fat tissue on gluteal regions, slight involvement of superficial muscle fibers of the greater gluteus on both sides is observed. **e.** Seven months post-operative.

vegetable, or animal] into the dermis or subcutaneous tissue for aesthetic purposes [83,84]. An improvement has been seen in local manifestations, but a specific immunomodulatory treatment for the manifestations related to foreign body modelling reaction and ASIA cannot yet be established.

The present study had some limitations. First, the starting sample size was small (two subjects did not return for follow up and one died during follow up). Unfortunately, given the small sample size, it was not possible to provide powerful results to assess causality. In addition, the small sample size was insufficient to detect clinically relevant differences (there were no unexposed patients) [85]. Given this, it was not possible to objectively differentiate between the clinical results of patients who had had previous aesthetic surgeries and those who had not, nor to establish a difference between the two groups with respect to the time of appearance of the ASIA syndrome. Secondly, four patients had a very low clinical ASIA score with the consequent difficulties in interpreting it. Nor was it possible to do a study with mass spectrometry to determine the characteristics of the injected unknown substance as Gordillo-Hernández et al. had done [8]. Furthermore, various familial immunological diseases were often underestimated.

5. Conclusions

In the present case-series, a group of patients exposed to biopolymers in the gluteal region and who developed foreign body modelling reaction is described, thus suggesting a chain-of-events relationship in the appearance of ASIA syndrome. Getting a complete clinical history including familial background and personal exposure to toxic substances is recommended because of the probable multifactorial association for the development of ASIA syndrome found in the present case-series.

Given that all the patients of this case series went to "clandestine" clinics and were treated by personnel whose training was unknown, it is important to consider the need for educational strategies to inform the public of the dangers and damage to one's health involved in going to "clandestine" clinics that provide aesthetic procedures. However, it is necessary to do other types of epidemiological studies focused on public health based on the geoepidemiology of the problem and apply stringent surveillance control.

It is likely that foreign body modelling reaction is a precursor in the spectrum of ASIA syndrome. However, it is necessary to do further well-designed, case-control or prospective cohort studies [86] (including exposed and unexposed subjects and a larger sample size) that would make it possible to analyze why some subjects develop ASIA syndrome

and other subjects stay asymptomatic in order to establish predictive models that could help prevent the onset of the disease. Last, but not least, the applicability and the timely use of the proposed surgical technique must be evaluated to see if it really produces an objective clinical improvement.

Ethical approval

This study was approved by the ethics committee for research on human beings HSJ-FUCS (CEISH). Act number 12/July 8, 2018.

Informed consent

Each patient was provided with a form to give written informed consent before participating in the study.

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Authors/Role participation

Montealegre G: Conceived and designed the study and interpreted the data, performed the surgery; drafted, revised the article, and approved its final version. He agrees to all aspects of the work.

Uribe R: Participated in the conception and the design of the study, participated in acquiring the data, performed the surgery; drafted, revised the article, and approved its final version. She agrees to all aspects of the work.

Rojas-Villarraga A: Made a substantial contribution on acquiring, analyzing and interpreting the data; did the clinical and rheumatological evaluations, drafted, revised the article, and approved its final version. She agrees to all aspects of the work.

Martínez-Ceballos MA: Made a substantial contribution on acquiring the data, analyzing and interpreting it; drafted, revised the article, and approved its final version. She agrees to all aspects of the work.

Declaration of Competing Interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.toxrep.2021.01.011.

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