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Modeling materials disease, adjuvant-induced autoimmune syndrome, and other vanity diseases

Enfermedad por modelantes, síndrome autoinmune inducido por adyuvantes y otras enfermedades de la vanidad

Brandon Rafael Contreras-Díaz,* Arturo Córdova-Gómez,* Leonardo Rubio-Gómez,‡ Rafael Contreras-Ruiz Velasco§

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Palabras clave: *adyuvantes, biopolímeros, granuloma, enfermedad autoinmune, siliconas, relleno dérmico.*

ABSTRACT

For a long time, simple, safe, and painless methods have been sought to improve body contour, using infinite materials ranging from solids to liquids. Thus, an epidemic of unknown magnitude has arisen, affecting both sexes between the third and fourth decade of life who, in their eagerness to look better, ask to be injected with "miraculous" substances such as silicone, vaseline, mineral or vegetable oil, etcetera. Not all present signs and symptoms that force them to consult; the sequelae can occur up to 30 years after the application. The risks of using these substances range from the simple migration of the application site, obtaining a different result to the desired one, to death, including reactions of rejection of the organism to the injected substance. Managing these patients is challenging for the physician since it needs to be standardized. Due to the diversity of substances used as fillers, predicting their behavior is difficult, so there is only partially satisfactory treatment. We conclude that, except for autologous fat, no innocuous substances should be applied to the body, and only certified plastic surgeons should be consulted.

RESUMEN

Durante mucho tiempo se han buscado métodos sencillos, seguros y poco dolorosos para mejorar el contorno corporal, al emplear infinidad de materiales que van desde los sólidos hasta los líquidos. Es así que ha surgido una epidemia de magnitud desconocida, que afecta ambos sexos entre la tercera y cuarta década de la vida que, en el afán de verse mejor, solicitan ser inyectados con sustancias "milagrosas" como: silicona, vaselina, aceite mineral o vegetal, etcétera. No todos presentan signos y síntomas que les obliguen a consultar, las secuelas se pueden presentar hasta 30 años después de la aplicación. Los riesgos del uso de estas sustancias van desde la simple migración del lugar de aplicación, con lo cual se obtiene un resultado diferente al deseado, hasta la muerte, debido a las reacciones de rechazo del organismo a la sustancia inyectada. El manejo de estos pacientes es desafiante para el médico, ya que no está estandarizado y, debido a la diversidad de sustancias usadas como relleno, es muy difícil predecir su comportamiento, por lo que no hay un tratamiento del todo satisfactorio. Concluimos que, salvo la grasa autóloga, no existen sustancias inocuas para ser aplicadas en el cuerpo y debería recurrirse solamente a cirujanos plásticos certificados.

* Surgeon, Universidad La Salle. Mexico.
‡ Resident of Plastic and Reconstructive Surgery, Centro Médico Nacional 20 de Noviembre. Mexico.
§ General Surgeon, ABC Medical Center. Mexico.

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INTRODUCTION

The desire to increase the volume of specific body areas for aesthetic purposes and to prevent and reduce skin aging has existed for a long time. Today, more than ever, people are seeking to achieve it. For a long time, surgeons have searched for simple, safe, and painless methods to improve body contouring, using an infinite number of materials ranging from solids (prostheses that require a formal surgical procedure) to liquids, such as kerosene, silicone, methyl methacrylate, polyacrylamide gel, among others.[1]

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Due to ignorance, lack of resources, or fear of a surgical procedure, people look for procedures that are not wholly accepted by orthodox medicine but that meet their expectations of having a low cost, not involving a scalpel, and even being able to be performed in the comfort of their home or an office, in the best of cases. To top it off, the interested party usually knows someone who has had it done some time ago and has yet to present any complications. This person usually encourages him/her to do it.[2]

According to the latest survey by the International Society for Aesthetic Plastic Surgery, in 2018, injectable treatments accounted for 76% of non-surgical procedures in the top 10 countries with the highest number of aesthetic procedures globally.[3]

Thus, an epidemic of unknown magnitude has arisen,[4] that affects patients who, in their eagerness to look better, request to be injected with "miraculous" substances, known as fillers, modeling,[5] biopolymers, "tissue implants", "expandable cell implants", or modeling, among others;[6] at a bargain cost, compared to anything that has to do with a scalpel, in addition to being able to perform it in different sessions, as your pocket allows and based on the results you get.

The substances used are classified into resorbable ones (hyaluronic acid, poly L-lactic acid, tricalcium phosphate, and alginate-coated polysaccharide) and non-absorbable (silicone polyacrylamide, polymethylmethacrylate) and other substances, such as vegetable oils, motor oil, beeswax, and animal fat.[3] The patient is often unaware of the material and quantity infiltrated and the complications of applying these substances.[4,5,7-10]

HISTORY

The use of fillers dates back to 1899 when Gersuy injected kerosene into the scrotum of a young man who had undergone bilateral orchiectomy for tuberculosis. The same author injected petrolatum into the nose to correct a saddle deformity. The method fell into disuse when tumors produced by this substance, paraphinomas began to appear, and in 1902, Eckstein reported its disadvantages and complications.[7,11] injected liquid silicone for cosmetic purposes became popular after World War II (1937-1945). From 1940 to 1950, in Europe and the United States, similar complications were observed with silicone injections, abandoned in the 1960s and 1970s by indications of the health services, such as the FDA in the United States. By 1962 another element was added to the arsenal for body modeling or correcting congenital disabilities or postmastectomy: breast prostheses filled with liquid silicone that, when broken by its thin cover, the silicone migration gave systemic manifestations of autoimmune type. As early as 1964, Miyoshi, in Japan, described the adverse effects produced by the use of the first breast prostheses and the infiltration of adjuvant substances, proposing the term human disease by adjuvant.[11-15]

In Mexico, one of the first reports about the problems caused by the injection of modeling agents was described by Ortiz Monasterio and Trigos in 1972, showing the experience with 186 patients with mammary injections of different foreign materials.[9,15]

Polyacrylamide has been used for the past 20 years; this material was introduced in the late 1980s in cosmetic surgery under various trade names. Official bodies, such as the Food and Drug Administration of China, banned its production, sale, and use due to all the reports of adverse effects received from 2002 to 2005.

Recently, with the FDA approval of AdatoSil 5000 and Silikon 1000 for ophthalmic use in the United States, silicone is being used legally, but off-label, as a skin filler.[16]

Coiffman, in 2008, reported 342 patients studied and treated in 10 years and coined the term iatrogenic allogenesis to qualify this disease.

In Mexico, since 2000, the plastic Surgery and Rheumatology Departments of the General Hospital of Mexico have been pioneers in the integral and multidisciplinary study of modeling disease. The results of the different study protocols that have been carried out since 2000 have broadened the knowledge of the natural history of this disease, its medical and surgical treatment,

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and the prognosis of a disease that is still unknown in many aspects.[8]

In 2011 Shoenfeld and Agmon-Levin introduced the term ASIA (*Autoimmune [Auto-inflammatory] Syndrome Induced by Adjuvants*).[13,14,17-19]

EPIDEMIOLOGY

It affects both sexes between the third and fourth decades of life. From 68.75 to 97% are women.[2,4,7,15,20]

In most patients, the areas infiltrated are buttocks (56-74.4%), breasts (16-47%), legs (24%), hips (17%), thighs (17-22%), face (6-11%), labia majora and penis, among other sites (2%);[2,8,13,21] 14-40% of patients infiltrate more than one area, and 40% do not know the amount infiltrated, which varies from 10 ml to 10 liters.[2,13,15]

In a study done at the General Hospital of Mexico, the infiltrated substances found were: mineral oil (41.4%), guaiacol (11.4%), liquid silicone (8.5%), vegetable oil (5.7%), automobile oil (1.4%), bovine fat (1.4%), vitamins (1.4%), and mixed substances (12.8%).[15]

The true incidence and prevalence are unknown, but it is quickly shaping into a public health problem, which is why this article is.[21]

Risks of the application of fillers, modeling agents, and biopolymers

The risks of the use of these substances range from simple migration of the application site,[4,16] obtaining a different result to the desired one, to death if they are accidentally injected into a blood vessel,[4,16,20] through the body's rejection reactions to the injected substance,[16,20] and even leading to infection, tissue necrosis, sterile abscesses, and autoimmune responses.[10,22]

Not all patients present signs and symptoms that require consultation, but sequelae can occur 10, 20, and even 30 years after application.[5,7,23]

In order to help patients make a better choice, they should be told that the effects of these substances, if they appear beneficial, should not be considered permanent. If unfavorable, they should be considered permanent.

The silicone-induced autoimmune rheumatic disease has been debated for several decades. In 2012 Vera-Lastra et al. reported a patient with Still's disease after he got silicone implants and a cohort of patients with the severe local and systemic disease after illegal use of oils and adjuvants for cosmetic purposes, all of whom had an autoimmune disease.[13]

PATHOPHYSIOLOGY

An immunoregulation disorder and alterations at the connective tissue level generate the disease caused by modeling agents. It is also considered that injecting these substances can precipitate autoimmune phenomena in susceptible individuals.[24]

The following are considered determinants in the occurrence of a reaction: tissue idiosyncrasy or hypersensitivity, nature of the substance and impurities, total amount and anatomical site, local trauma and distant infections, and nutritional or vitamin deficiencies.[4,11,20]

The mechanisms associated with the immune response are related to the immunological transformation of self-antigens, secondary to a chemical, physical or biological alteration, or with foreign antigens that induce an immune response that produces a cross-reaction with the self-antigens creating an inflammatory or immune response of rejection, with cutaneous necrosis, migration of the material, thinning of the tissues and fibrosis with hardening and encapsulation of the material.[8,12]

The result of the injection of these substances is the replacement of normal tissue by cystic spaces of variable size that appear empty when stained with hematoxylin and eosin; with special stains such as Sudan, Nile blue or osmic acid, the encysted oils can be visualized, and the macrophages present their vacuolated cytoplasm, indicating that they have phagocytosed the foreign substance. This chronic inflammation results in the formation of granulomas. At the dermis level, there is thickening with an accumulation of collagen fibers oriented parallel to the superficial epithelium, with increased spindle fibroblasts; fibrosis

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subsequently involves the subcutaneous adipose tissue, resulting in a thickened dermis.[4,24]

CLINICAL PICTURE

The clinical presentation is variable in symptomatology, severity, and presentation time. Signs and symptoms can be local, systemic, acute, chronic, controllable, or lethal. Systemic signs and symptoms can be immunologic and non-immunologic.[5,7,11,22]

Inert substances, such as liquid silicone, always induce clinical manifestations in the long term (two to 25 years) and are of lesser severity if infiltrated in scarce to moderate quantities. However, even in small quantities, the more impure oily substances (edible, automobile, mineral oils, etcetera) always cause very early and much more severe clinical manifestations, although more localized.[2,8,15]

The most common general symptoms are pain, fever (45%), arthralgias (36%), myalgias (8.5%), polyarthritis (8%), Raynaud's phenomenon (2.8%), somnolence, malaise, and depression.[2,7,15,16,20,23] According to Coiffman, these last from one to two weeks with periods of exacerbation every two to three months.[7] Antihistamines and non-steroidal anti-inflammatory drugs shorten the duration of symptoms.[7]

The most common local clinical manifestations are signs of inflammation such as edema, erythema (68.5%), hyperemia (68%), pain (62.8%), irregularities, nodules (61.4%), thickening of the skin and subcutaneous tissue (55.7%), hyperpigmentation (54.2%), venous neoformations (34.2%), other inflammatory changes (54.2%), migration of the infiltrated substance causing regional lymphadenopathy, even at great distances and counter gravity,[8] in early stages (27.4%) and in late stages (80%);[2,6,15] keloid scars, hypopigmentation, ulcerations, hardening, necrosis, sclerosis, fibrosis; infection and fistulas draining whitish or oily material that take months to years to heal, in addition to contracture and deformity of the area.[4-9,11-13,16,21,23,24]

In 73% of cases, all these reactions preceded distant or systemic manifestations.[14] They can occur from months to 30 years after the injection, the average being six years,[2,4,8,9] in 73% of cases, they worsen during the menstrual cycle,[16] and in 3% of men after the application of hormones.[15]

Systemic complications include acute pulmonary edema, embolism, and death from the accidental intravascular injection.[20] Systemic granulomatous reactions include acute pneumonitis, granulomatous hepatitis,[5,8,11,24] and renal failure following injection of large quantities.[4,11]

In breast infiltration, migration is by gravity to the abdomen and the lymphatic route to the axillary nodes. In gluteal infiltration, migration is by gravity towards the thighs and legs and, depending on the depth of the infiltration, the substance can be deposited on the fascia and then affect only the skin or under the fascia and additionally affect the muscle; there is also lymphatic migration, causing inguinal adenomegaly and progressive accumulation of the substance at the dorsolumbar level.[15]

Autoimmune diseases related to these substances have been described, appearing on average after three years, such as progressive systemic sclerosis, systemic lupus erythematosus with cutaneous, hematologic, articular, and renal involvement; rheumatoid arthritis with nonspecific manifestations; mixed connective tissue disease, autoimmune hepatitis, primary biliary cirrhosis, Sjögren's syndrome, thyroiditis, serositis, vasculitis, scleroderma, and morphea,[5] coining the term human adjuvant disease to describe these cases,[5,11,18,19,24] and more recently ASIA.[18,19,22]

Disease progression is variable, with periods of relapse and remission. Clinical improvement is observed after surgery and steroid administration.[13]

DIAGNOSIS

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The clinical diagnosis is based on the symptoms plus the history of the application of a modeling substance and biopsy.[8] The complete study of the patient should include chest tele radiography to rule out pulmonary involvement.[11,14] The extent of the infiltration is determined by nuclear magnetic resonance.[8,13-15,24]

The most common laboratory abnormalities are anemia, polyclonal hypergammaglobulinemia, elevated erythrocyte sedimentation rate (ESR), positive antinuclear antibodies (ANA) with titers ranging from 1:80 to 1:1,024, rheumatoid factor with titers between 1:80 to 1:280.[18] Other studies that may be requested include C-reactive protein (CRP), fibrinogen, calcium, lactate dehydrogenase (LHD), angiotensin-converting enzyme, serum protein electrophoresis, antinuclear antibodies, C4, CH50, CD4+/CD8+ ratio.[14] Pathology findings are similar between cases, regardless of the infiltrating substance:[7,24] "fibrosis and chronic foreign body type inflammation", "granulomas", "numerous clear vacuoles, of different size surrounded by lymph histiocytic infiltrate", "foamy looking histiocytes containing material that refracts with polarized light and causes a vacuolated appearance", "dystrophic calcification". These chronic inflammatory changes result in the formation of foreign body granulomas.[4,9-11,13,16,24] The granulomas show large numbers of macrophages, giant cells, and, to a lesser extent, B and T lymphocytes.[14] "By pathological anatomy, it is impossible to identify the injected substance".[7] Structural damage of the dermis is characterized by thickening with the accumulation of collagen fibers and an increase in the number of fibroblasts and fibrosis of the soft tissues beyond the original area of infiltration.[24]

Shoenfeld's recent description of ASIA includes criteria for its diagnosis shown in *Table 1*.[13,17,19]

Mammary gland modeling disease presents a broad clinical spectrum of affection that, until recently, had not been categorized to facilitate its study and treatment. Priego et al. have proposed a classification of mammary modeler disease, as well as its treatment, according to stage.[24]

Torres and collaborators created an instrument to stage the damage produced by infiltration by modeling substances; they take into account the amount of infiltrated substance, number of infiltrated areas, infiltrated substance, symptomatology, signs, and results of laboratory studies and nuclear magnetic resonance, with which they propose a classification of four stages, shown in *Table 2*.[21]

TREATMENT

Managing these patients is challenging for the physician,[4] since it needs to be standardized[7,8] and, due to the diversity of substances used as fillers, it is complicated to predict their

Table 1: Diagnostic criteria for ASIA.

Major criteria	Minor criteria
Exposure to an external stimulus (injection, vaccines, silicone, adjuvant) prior to clinical manifestations The appearance of typical clinical manifestations: • Myalgia, myositis, or muscle weakness • Arthralgia and arthritis • Chronic fatigue, non-restorative sleep, and sleep disorders • Neurological manifestations (demyelination) • Cognitive impairment, loss of memory • Fever, xerostomia Removal of the initiating agent produces enhancement against the suspected adjuvant	Occurrence of autoantibodies or antibodies against the suspected adjuvant HLA suspected Autoimmune disease

ASIA = Autoimmune/inflammatory Syndrome Induced by Adjuvants. HLA = human leukocyte antigen system.

Table 2: Stages of infiltration damage by modeling substances.

Stage	Forecast	Features
1	Good	Excellent response to rheumatological-pharmacological treatment (combining different substances such as methotrexate, prednisone, colchicine, and folic acid). They respond in less than four months. Most of them do not require surgical treatment. Recurrences can be treated in the same way. An excellent long-term response is expected
2	Reserved	They usually have an excellent response to pharmacological treatment after about six months. After that time, the infiltrated tissues will show favorable changes, making them candidates for scheduled surgical treatment to remove most affected tissues. Reconstructive options for these patients are usually successful
3	Limited	Their response to treatment is limited; they temporarily improve their conditions but have increasingly frequent symptomatic periods, which limits the possibility of receiving repeated pharmacological treatment. As soon as their general conditions improve, they should undergo surgical treatments to remove most of the infiltrated tissues in one or several surgeries and try to improve their quality of life by eliminating most of the infiltrated substances from their body. Reconstructive options in these patients are more limited because they present a higher degree of involvement and have a high incidence of complications related to poor healing and increased tissue friability
4	Poor	Poor short-term prognosis, very severe, and may die of multiple organ failure. In these patients, there is no good response to the usual pharmacological treatment, as it can be aggressive and aggravate the patient's conditions, so they are not candidates for surgical treatment; emergency hospitalization is recommended

behavior.[7] Hence, there is no completely satisfactory treatment. In addition, it is a poorly described pathology,[8] and up to this moment, it is considered incurable since it is impossible to eliminate the substances infiltrated in the tissues.[6,15] World reports, in general, support conservative management.[24]

Coiffman recommends that only very localized and encysted masses should be resected. The skin should be protected with emollient and anti-solar creams,[6] avoiding massages as they do not dissolve the masses and, like corticosteroids, thin the overlying skin. Conventional liposuction, as well as ultrasound or vibratory electric massages, do not help.

Among the most commonly used medical treatments are non-steroidal anti-inflammatory drugs,[5,8,12,25] intralesional[2], and systemic steroids,[4,13,14,25] such as prednisone at variable doses;[8] colchicine at doses of 1-2 mg/day,[2,13] antibiotics,[5,12] the most frequent being minocycline; cytotoxic drugs, cyclosporine;[4] immunomodulators such as imiquimod cream[16] and etanercept.[4,5,8,16,25] They are managed with methotrexate at variable doses (7-10 mg/week) together with folic acid for four months, evaluating the evolution of these patients and continuing their treatment, decreasing or increasing the doses according to the individualized response.[8,13] Other drugs used are cyclophosphamide, chloroquine, and D-penicillamine.[13,14]

Once the Rheumatology Service assesses a favorable evolution or response with pharmacological treatment, observing the decrease of local and general signs and symptoms, the Plastic Surgery Service reevaluates the patient to propose surgical reconstruction, provided that the quality of skin and tissues is manageable and reliable for a surgical procedure and that the patient has understood his disease not only in a physical scope.[8]

Part of the integral management is the assessment of psychological treatment since this disease has a self-induced origin due to dissatisfaction with the aesthetic aspect of their own body or distortion of the self-

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image.[8] It is also desirable that they get support because managing complications can lead to results opposite to what they initially sought, with a more significant self-esteem deterioration and guilt.

Some surgeons specialize in removing the injected material using different surgical techniques, with which most show clinical improvement. However, there needs to be more experience. Due to the migration they usually present, they can only be partially removed when applied in large quantities because they require a complex mutilation and repair process.[2,4,5,12,16] When ulceration occurs at the application site, antibiotics and other drugs are additionally administered, reducing the inflammatory symptoms but not the clinical picture.[2,13]

If the mass is small and deeply embedded, it is preferable to leave it under observation; if they are huge and infiltrating masses, it is advisable not to treat them, as reconstruction would leave severe deformities,[2,7] as it requires extensive resections, since, in general, the substances affect the entire anatomical region involved and are very disseminated, because, with time, gravity and pressure cause the material to migrate. In addition, the resection generates important skin covering defects, requiring grafts or flaps of various sizes and, generally, with poor and disappointing esthetic results for both patient and surgeon.[8]

In patients infiltrated in the breast and presented complications, the most commonly used treatment was subcutaneous mastectomy with immediate or delayed reconstruction using silicone prostheses. However, they had a limited esthetic result. They presented a considerable number of complications,[9,12] and even so, none of the procedures has been able to eliminate the compromised tissues and definitively solve their effects.[23] All patients with breast disease due to modeling agents in the study by Priego et al. were managed in conjunction with the Rheumatology Service for the medical treatment of human disease due to modeling agents.[24]

In pelvic limb cases, immunosuppressants, non-steroidal analgesics, and the controlled sub-atmospheric pressure system are used to avoid extensive debridement that leaves bloody areas that are difficult to manage due to bleeding and chronic multidrug-resistant infections that can cost the patient's life.[1]

Iatrogenic allogenesis does not physically kill the patient but destroys the patient's psyche, self-esteem, and quality of life,[7] of which are also complications.

DISCUSSION

There is medical literature endorsed by prestigious publishers in which the use of these substances in mice is mentioned, in which no elevation of immune response was found after application of the substance. An example of this literature is *Almir Moojen Nácul's Bioplasty, the Interactive Plastic*, where reference is made to using PMMA (polymethyl methacrylate) to carry out this type of procedure.

Suppose a substance is capable of providing volume and contour in various body areas. In that case, it must be chemically and physically inert, non-allergenic, non-carcinogenic, not cause inflammatory or foreign body reactions, not migrate from the site where it is applied and be affordable. For this reason, various materials have been used, such as liquid silicone, collagen, methyl methacrylate, and polyacrylamide gel, which, after some time, have not proven to be effective because they cause complications. All these products also create an autoimmune reaction that produces histological changes consisting of the appearance of macrophages containing vacuoles of oily material in their cytoplasm in the initial stages and later the formation of granulomas. The undesirable effects can appear up to several decades after application, causing them to be used in patients without fully knowing whether undesirable effects will appear. When studying what has happened with this type of substance, clinical trials should have a duration of 50 years before declaring the material under study innocuous. Unfortunately, not every laboratory will recover the money invested in research before that long. Such was the case with Bio-Alcamid.

There are already reports that silicone breast implants can trigger autoimmune reactions,

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with the advantage that, if present, they can be removed.

History shows that not even the substances created and elaborated by pharmaceutical laboratories have been innocuous, let alone those not for medical use, used clandestinely. The idealization of the figure, as well as its value, causes a strong demand for substances for this use and those who apply them. The excess demand and scarce supply push prices upwards, making them attractive to professionals and non-professionals alike. Even for professionals, it will be difficult to distinguish the formal literature and the serious laboratories, and because they are well-remunerated, decisions will be biased.

The simplest thing to conclude would be that, except for autologous fat, there are no innocuous substances to be applied in the body, so if a patient persists in the idea of having them applied, he/she should only resort to certified plastic surgeons, who have already been established for some time, and that only autologous fat or substances that can be removed in their entirety if necessary, with a prior signature of informed consent, which should be kept indefinitely, taking into account that undesirable reactions can occur decades later.

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Correspondence:
Brandon Rafael Contreras-Díaz, MD.
E-mail: rafa.contdz@gmail.com

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