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ABSTRACT: The human adjuvant disease arises as a complication after the infiltration of molding substances used for cosmetic purposes. The severity of clinical manifestations depends on the amount and type of agent used and usually present as hyperemia, pain, nodules and thickening of the skin. Short-term symptoms are mostly transitory with short lasting effects while most common late complications present as infection and hypersensitivity reactions to the infiltrated material. Most commonly used substances are: paraffin, silicone, hyaluronic acid, collagen and vaseline. Clinical diagnosis in primarily based on the precedent event of having any modeling substance applied. The diagnosis is confirmed using histopathology, finding alterations in both dermis and hypodermis. The combination of patients having unrealistic expectations from these procedures and the ignorance and neglect of the adverse effects when applying these agents highly increases the morbidity and mortality.

Keywords:
Human adjuvant disease, autoimmune diseases, connective tissue diseases, fillers, adjuvant substances.

Review Article

Plastic Surgery

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Introduction

The application of modeling agents for body shaping, correction of deformities or enhancing corporal attributes is an increasingly common practice in Mexican society, in many cases, not properly assessing the specificities of each substance and harmful effects it can have in the patient's body. The human adjuvant disease is an autoimmune disease, resulting from the infiltration of various substances with aesthetic purposes. [1,2] **Table 1**. Most of the patients suffering from this ailment are not even sure which was the substance infiltrated on their bodies and its possible complications.

The use of modeling substances has its origins in the seventeenth century, being Balzer in 1886 that wrote the first report about the use of modeling substances, being oily substances the cause of cutaneous induration. [2] In 1899, Gertsuny described paraffin-based prosthetics in patients with secondary testicular orchiectomy tuberculosis, as well as in patients with cleft clip and palate. In the early 70's, due to the adverse effects that were observed, the FDA suspended the use of substances modeling, however, they continue to be widely used in several countries, including Mexico. [3]

During the 1970s, Dr. Ortiz Monasterio was the first to report a series of clinical cases where, due to the use of infiltration of modeling substances in the mammary gland, reconstructive treatment was necessary, with difficult management and an unclear or unfavorable prognosis. [4]

Epidemiology

During a study conducted with the population of the General Hospital in Mexico from 2000 to 2009, as reported by Torres and cols, the proportion of people affected by this pathology was 3:1 with predominance in women, mainly in their third decade of life. [1]

The popularity of these aesthetical procedures also allures patients seeking low-cost procedures, sometimes performed by unqualified personnel in unauthorized places, regardless of the irreversible damage that these products may cause to their physical health, self-esteem and their future life quality. [5]

In the 1980's, the introduction of collagen began a new era of minimal of invasive cosmetic procedures. During the first days of the use of collagen, some

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Material	Group	Mechanism
Collagen	Fibrous protein	Shaped fiber bundles structure is responsible for providing the extracellular tissue its tensile strength and elasticity.
Synthetic hydroxyapatite	Calcium phosphate	This material allows the overgrowth of bone; it is not osteogenic.
Polytetrafluoroethylene	Polymer	Support and soft tissue isolation, it creates a space occupied by the clot and allows grown factors accumulation that promote bone formation.
Hyaluronic acid	Glycosaminoglycans	Retain water molecules intercalated in its structure. A most water, hyaluronic acid is the most widespread molecule.
Methacrylate (liquid silicone)	Polysiloxano	Induces a collagen fibrous capsule around the product.
Vaseline	Alkanes	Inert material which when inserted causes increased volume of the skin.

Table 1. Types and characteristics of biopolymers.

industry analysts estimated the entire market for dermal fillers could produce potentially $40 million in revenue. In the 1990s, collagen kept on controlling the market of fillers in the USA, while international hyaluronic acid (HA) fillers emerged as the new leaders in the market due to the longevity, performance and handling advantages when compared to collagen. By 2010, more than 50 different fillings were in the market in several European countries. Taking into account all forms derived and modified viscosities; the number may be much higher now. [6]

Clinical Features

The severity of symptoms depends on various factors, such as the amount and type of substance injected, place of infiltration, hormonal situations, concomitant diseases and genetic disposition. In many cases, neither the patients nor their family are certain about which substance was used in the procedure, so imaging studies such as spectrometry nuclear magnetic resonance has been designed to identify and study their characteristics, based in the separation of states of the nuclear spins in the presence of an intense magnetic field, [2] showing the distribution in different tissues of hydrogen nucleus in the water. Recognizing the three-dimensional molecular structures thus is the substance identified to define treatment and develop a prognosis. The onset of clinical manifestations is usually insidious, with local and systemic clinical changes. Laboratory studies suggest an autoimmune-like connective tissue diseases,[2] with periods of fluctuating symptoms and an unpredictable prognosis.[1]

Complications

Patients who suffer from early complications (such as redness, swelling and itching) can be as high as 80% usually a direct result to the improper placement of the load and localized reactions at the injection sites. The short-term complications are mostly transient and disappear with few lasting effects. Late complications are the result of infection and hypersensitivity reactions to the fill materials, which can lead to inflammation, pigmentation and necrosis. Chronic complications may appear in the form of ulceration and granulomas.[7] Complications may include changes in the color, texture and temperature of the skin, granulomatous inflammation, skin nodules, fistulae, spasms, arthralgia, pain and deformity. **Table 2.** The intensity of the inflammatory reaction depends on a variety of factors such as: tissue hypersensitivity, nature of the substances and impurities, total amount an infiltrated anatomical sire, local trauma and distance infections, coupled with nutritional or vitamin deficiencies.[2] Biopolymers and liquid silicon for instance, are more likely to have long-term manifestations (2-25 years later), with more generalized symptoms such a joint pain and substance migration, while oily substances cause earlier (months) and more aggressive and localized manifestations[1] . Early recognition is vital. If the swelling is fluctuating, the purulent material must be drained and sent for culture and sensibility tests. If it is not, the recommendation is to start patients on antibiotics (macrolides and quinolones). Macrolides have been effectively found to prevent the formation of a biofilm. Should this line of treatment fail, a high-dose on injected steroids can be considered (Triamcinolone – Kenalog 20-40 mg/ml) as they help to control chronic inflammations associated with more severe injuries. Excision is the last step.[7]

Pathophysiology

When studying the inflammatory response, we find spontaneous intracellular synthesis of IL-15 by macrophages and increased production of hyaluronic acid by fibroblasts; the association between autoimmune diseases and the injection of modeling agents is surprisingly common. The outcome from injecting a lot of these agents is well known; normal

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Modeling material	Year	Typical uses	Safety	Complications
Paraffin	1890	Depressed scars, nose, varicose veins and hernias.	Ineffective	Inflammation, tissue necrosis and tenderness at the injection site.
Petrolatum	1900	Nose, testis, cheeks, breasts.	Ineffective	Tissue necrosis, air embolism, tenderness and skin ulceration.
Camphor	1920	Soft tissues (buttocks and breasts)	Ineffective	Soft and painful tumors.
Silicon	1960	Soft tissues (buttocks and breasts)	Effective and safe	Cyst with variable morphology surrounded by a thin fibrous capsule. Pain, edema, erythema, bruising and hyperpigmentation.
Mineral oil	1970	Scrotum and soft tissue (buttocks and breasts)	Ineffective	Polyarthritis, panniculitis, arthralgia
Guayacol	1988	Buttocks, breasts calves	Ineffective	Panniculitis, progressive systemic sclerosis, chronic active hepatitis
Polyacrylamide	2000	Buttocks, breasts, calves and facial corrections.	Effective and safe	Granulomas, partial necrosis, telangiectasia, functional disorders and inflammatory reaction.

Table 2. Use of Modeling materials

tissue is replaced with cystic spaces of various sizes that are empty when stained with hematoxylin and eosin. Using special stains such as; Sudan, Blue Nile or osmic acid, the entrenched oils are displayed and macrophages present their vacuolated cytoplasm, indicating that they have phagocytosed the foreign substance. This chronic inflammation leads to the formation of granulomas.[3,5] At the dermis level, the alterations present as thickening with accumulation of collagen fibers parallel-oriented to the superficial epithelium, with an increase in the number of spindle-shaped fibroblasts, in time the fibrosis involves the subcutaneous adipose tissue, resulting in a thickened dermis. [8]

Histopathology

When studying the acute inflammation state, we can find several histological alterations; the exudative phase is characterized by an infiltration of polymorphonuclear while in the chronic phase the infiltration of lymphocytes, plasma cells and fibroblasts is predominant (this alteration may be found after 18 months of observation) other alterations such as macrophages filled with vacuoles and the disappearance of silicone in infiltrated sites, commonly known as "ghost spaces" have been described. [3] During the 1990s in Mexico, several studies were conducted to better understand several aspects of this entity, Dr. Medina did a study that identified specific autoantibodies to this disease, Dr. Sánchez Guerrero conducted an epidemiological and histopathological study in patients with silicone breast implants, and Dr. Cabral documented the appearance of cytokines (IL-1) in affected patients. [4]

The human adjuvant disease is very specific to modeling substances for medical use such as liquid silicone, however there is a wide variety of unauthorized modeling agents such as mineral, vegetable and industrial oil which are known for having serious consequences but at the same time little information can be found or described in literature. [4] It is most likely that these substances act as superantigens and trigger the unfolding of systemic autoimmune diseases of the connective tissue in genetically predisposed patients.

Discussion

The human adjuvant disease, caused by the introduction of foreign substances in the body for aesthetic modifications, mainly affects women between 30 – 40 years old with a ratio of 3:1 compared to men. The most frequently used products are mineral oils such as petrolatum or paraffin; animal fats such as lanolin and beeswax; vegetable fats such as cottonseed oil, olive, sesame, sunflower, sesame and camphor; oils for industrial and mechanical use, liquid silicone and collagen.[9,] [10], sometimes identification of the agents used has not been possible.[11] The majority of people (60%) was unaware of the type of substance infiltrated; however, they described as transparent, odorless, oily, which was often measured by bottles or syringes of 60 ml. The rest of the substances identified by patients included: mineral oil (41.4%), guaiacol (11.4%), liquid silicone (8.5%), vegetable oil (5.7%), motor oil (1.4%), bovine fat (1.4 %), vitamins (1.4%) and mixed (12.8%).[24] Usually, the objective is to improve anatomical areas, in most patients, the infiltrated sites were: buttocks (56%), breast (47%), legs (24%), hips (17%), thighs (17%), face (11%) and elsewhere (2%), there have been reported cases of paraffinomas in orbit and eyelids, scalp and external genitalia. 40% of the

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patients had various infiltrated areas[6], and 40% did not know the amount infiltrated although it ranged from 10 mL to 10 liters; 35% were applied a liter, 15% from two to five liters, 3% six to eight liters, and nearly 5% more than eight liters. The time between infiltration period was one day to one month, with an average of two to three injections per patient. [3] Clinical manifestations of symptoms has a very lengthy time lapse; sometimes it can be weeks, months or even years; however, some cases have been reported 30 years after the application.[10] Local symptoms include increased temperature, recurrent erythema, hyperpigmentation or changes in skin texture. When observing the injection area, irregular nodules varying in depth and density, sometimes they can be infiltrated, with an irregular contour and painful to palpation. These lesions may ulcerate creating fistulas draining oily material and even cause other injuries distant from the initial infiltration area. [11] The combination of ignorance about the irreversible side effects these agents will cause and the false expectation from patients wanting immediate results account for the emergence of incurable pathologies, which gravely affect the patients health and quality of life.[1] The use of silicones as injectable material was initially described by McDowell-Duffy and was introduced in 1965, primarily as PDMS polymer. They have been widely used in cosmetic treatments for soft tissue augmentation and correction of facial defects. Liquid silicone was initially seen as a biologically inert material; however, it has been linked to several adverse inflammatory reactions. These reactions largely depend on the administration technique, for instance; when small volumes of pure silicone droplets are introduced with sterile technique, complications are rare as compared when large amounts of adulterated material are injected in patients with specific risk factors. Among these factors we consider; tissue hypersensitivity or idiosyncrasy, nature of the substance and impurities, amount and anatomic site, local trauma, infections distance and nutritional or vitamin deficiencies. In 1992 a possible link between silicone implants and autoimmune diseases was considered however, epidemiological studies [12-14] and meta-analyzes [15] did not support this association, in 1995 the American College of Rheumatology concluded that silicone implants did not represent a demonstrable additional risk for rheumatic disease. The Food and Drug Administration recommends that all patients with silicone implants, made a periodic review of MRI to evaluate leaks, three years after the first implant surgery and every two years thereafter, there is also another group of experts that suggest MRI should be used as a confirmatory diagnostic test and not to evaluate asymptomatic patients.[16,17] Infections in these breast implants occur approximately 2-2.5% of cases,[18,19] founding primarily gram positive pathogens such as coagulase-negative staphylococci, Propionibacterium species, S. aureus, streptococci and Mycobacteria. [20-22] It has been reported that the presentation of anaplastic large cell lymphoma in the capsule adjacent to the silicone implants can be up to 18 times higher when compared to the population without implants, according to a case-control study.[23] Although the data obtained in the Netherlands only 11 cases were reported in a period of 17 years, further studies are needed to demonstrate the above causal relationship. Polyacrylamide has been used during the past 20 years globally, yet it is a new product in countries such as Ukraine, Russia and China. This material was introduced in late 1980 in cosmetic surgery under various trade names such as: Royamid (Ukraine), Interfall and Formacryl (Russia). The complications when using this product manifested from several months up to three years after it was injected, they included product migration induced by gravity, formation of granulomas with ulceration and fistula formation, infection, pain and deformity of the injected area. The treatment in these cases is the removal of the injected material, when possible, by suction or resection of the damaged area, although many times this procedure is differed as it is a mutilating surgery and with unaesthetic outcome.[7] After reviewing the documented the medical records of 279 patients diagnosed with human adjuvant disease [3] in the database service of the General Hospital of Mexico in the Plastic and Reconstructive Surgery and Rheumatology, clinical diagnosis is mainly based on the precedent of a modeling agent application, the most common local manifestations were hyperemia (68.5%), pain (62.8%), nodules (61.4%), thickening of the skin and subcutaneous tissue (55.7%), hyperpigmentation (54.2%), venous neoplasms (34.2%), other inflammatory changes (54.2%) and migration of the infiltrated substance from the injection area with early onset (27.4%) and late onset (80%).[6-11] Most common systemic symptoms are fever (45%), arthralgia (36%), myalgia (8.5%), polyarthritis (8%) and Raynaud's phenomenon (2.8%). Most histological alterations were observed in the dermis and hypodermis where the agent was injected, the findings are multiple cystic spaces with aspect of "Swiss cheese" with dense fibrous tissue around these areas, inflammatory cells, including foreign body giant cells, lymphocytes, polymorphonuclear leukocytes and macrophages, which show phagocytosis of the foreign substance. These chronic inflammatory changes result in the formation of foreign body granuloma. [24] Treatment include the prescription of NSAIDs, intra lesional and systemic steroids with variable doses of prednisone, colchicine dose 1 to 2 mg / day, antibiotics such as minocycline, cytotoxic, imiquimod cream and etanercept. In small lesions, complete removal of

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foreign material is effective using surgical solutions, when presented with larger defects, flaps and or grafts were used during the reconstructive procedures. [8]

Conclusion

Regardless of the FDA prohibitions and recommendations, the use of modeling agents for cosmetic purposes is present all socioeconomic strata, mostly without the proper regulation by the pertinent national institutions and they are in continuous use despite the knowledge about the serious consequences they produce has been documented for over 50 years. Ignorance by patients with aesthetic illusions and neglect from physicians not fully knowing the pathophysiological features or adverse effects of substances used, when undergoing such procedures, directly increased morbidity and mortality ratios. The severity of clinical manifestations varies according to the amount and type of substances injected along with the patients genetic predisposition. Due to the low incidence of the disease by modeling agents there are little case reports and the follow up specially in the long term monitoring with the lengthy manifestation of symptoms accounts for a difficult and proper documentation of possible side effects.

Conflicts of Interests

The authors declare no conflict of interest.

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