

ORIGINAL ARTICLE

A case series and a review of the literature on foreign modelling agent reaction: an emerging problem

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Abstract

Foreign modelling agent reactions (FMAR) are the result of the injection of unapproved high-viscosity fluids with the purpose of cosmetic body modelling. Its consequences lead to ulceration, disfigurement and even death, and it has reached epidemic proportions in several regions of the world. We describe a series of patients treated for FMARs in a specialised wound care centre and a thorough review of the literature. A retrospective chart review was performed from January 1999 to September 2015 of patients who had been injected with non-medical foreign agents and who developed cutaneous ulceration needing treatment at the dermatology wound care centre. This study involved 23 patients whose ages ranged from 22 to 67 years with higher proportion of women and homosexual men. The most commonly injected sites were the buttocks (38.5%), legs (18%), thighs (15.4%) and breasts (11.8%). Mineral oil (39%) and other unknown substances (30.4%) were the most commonly injected. The latency period ranged from 1 week to 17 years. Complications included several skin changes such as sclerosis and ulceration as well as systemic complications. FMAR is a severe syndrome that may lead to deadly complications, and is still very common in Latin America.

Introduction

For over a century, physicians and patients alike have been interested in the subcutaneous injection of high-viscosity fluids and other substances for the restoration and improvement of body contours (1). The first report on the use of a foreign substance for modelling dates back to 1900: Gersuny used paraffin for testicular prostheses in a patient who had undergone bilateral orchiectomy for testicular tuberculosis (2,3). After this report, the use of paraffin as a modelling agent became widespread, and almost simultaneously reports on delayed reactions to these substances began to appear (4–7). Some complications from the use of paraffin included aesthetic failure, migration, ulceration, fistulae, infection, necrosis, inflammatory granulomatous

reactions, pulmonary embolism and death (8–10). The term paraffin granuloma or later paraffinoma was coined to describe

Key Messages

- foreign modelling agent reaction (FMAR) is a devastating syndrome steadily reaching epidemic proportions
- a retrospective review of FMAR cases and a comprehensive literature summary on FMAR were performed
- FMAR is more common in women and homosexual men, and causes severe complications that range from local reactions and ulcerations to systemic complications and even death
- the most commonly affected areas are the buttocks, lower extremities and breasts

the histopathological changes in the biopsies of these patients (9).

Post World War II, there are reports of Japanese women using industrial-grade liquid silicone for breast augmentation. At the same time, medical-grade silicone made its appearance in the USA and Mexico, gaining widespread popularity (6,10,11). The complications that followed were often more severe than those seen with paraffin. Industrial-grade silicone contains additives that lead to tissue necrosis. In addition, injectable formulas often included additives designed to create a fibrous reaction. The infamous Sakurai formula is an example of an injectable formula that produced extensive fibrosis with concomitant tissue destruction (11). Medical-grade silicone was also widely used for body contour modelling despite the fact that it was never approved by the Food and Drug Administration (FDA) for this indication.

In 1964, Miyoshi *et al.* proposed the term human adjuvant diseases (HADs) to describe the systemic reactions to silicone injection (12). An adjuvant is defined as a material that prolongs and enhances the production of antibodies by extending the presentation of an antigen to the immunologic system, a phenomenon triggered by toll-like receptor activation (13–15). They reported two cases of connective tissue disease-like disorders, characterised by lymphadenopathy, fever, subcutaneous nodules, arthralgias or arthritis, Raynaud's phenomenon and autoantibodies in patients who had undergone breast augmentation with injections of paraffin or related substances. HAD could develop years after the administration of injection (12,13,16–18).

Initially used only by plastic surgeons in the USA, silicone eventually became a popular injectable for individuals outside the medical profession. In 1991, the FDA issued guidelines forbidding the marketing or sale of injectable liquid silicone for aesthetic injection and officially banned its use (19,20). The sale or injection of liquid silicone is currently considered a felony in the state of Nevada (6). Strangely enough, the FDA continues to approve dermal fillers that cause severe reactions (21,22).

Other substances, beside paraffin and silicone, that have been reported to cause foreign modelling agent reactions (FMARs) are vegetable oils, car engine or transmission oil, guaiac oil, lanolin, bee's wax, animal fat, polymethylmethacrylate, polyglactin and polyalkylimide (1,6,15,23–32).

In some regions of the world, such as Latin America and Asia, FMAR has reached epidemic proportions because of the absence of regulations and government corruption (26,33). Brazil, Argentina, Venezuela, Colombia and Mexico lead the FMAR epidemic. A recent study in Colombia reported that 341 patients developed this syndrome over a course of 10 years (34). In Mexico, a single case series from Mexico's General Hospital (MGH) analysed 179 patients with FMAR and another retrospective study reported on 279 patients (35,36). The number of patients seeking medical help for FMAR is steadily increasing. At the MGH, an average of 30 patients are seen per week (36). This may indicate that the prevalence of FMAR is much higher, but unfortunately epidemiological data is absent. Sporadically, case series are reported in many countries around the world. In the Netherlands, FMAR is common among transsexuals (31).

The purpose of this case series is to present significant findings from patients who sought attention at the Interdisciplinary

Wound and Ostomy Care Center (IWOCC and Dr Manuel Gea Gonzalez General Hospital (Mexico City, Mexico), to offer a critical review of the literature and provide evidence for the use of the term FMAR.

Methods

A retrospective review was carried out to study clinical and histopathological features of patients with FMAR who were treated from January 1999 to September 2015 at the IWOCC. Patients were included if the diagnosis of FMAR had been confirmed by either biopsy or a definitive clinical history and where medical records, biopsy or any other form of records had at least the patient's age, sex, ulcer location and characteristics. Any other relevant data were also recorded.

We excluded patients who had foreign body reactions to injection or FDA-approved facial fillers. Available biopsies or imaging studies were reviewed for additional information on the nature of the foreign modelling agent.

Results

After a review of the charts, photos and biopsies, we were able to locate 23 patients who met the criteria. Of the 23 patients, 10 (43.48%) were men and 13 (56.51%) women. At the time of consultation, the patients were on average 38 years old (22–67). Full charts were available for review only for 11 patients.

Nine of the patients (39%) were injected with mineral oil, five were told that the injections were collagen (11%), one (4.3%) was injected with guaiac oil and one was told it was cod liver oil. One third (30.4%) were ignorant of the injected substance.

The most frequently injected regions included buttocks (38.46%) (Figure 1), legs (17.95%), thighs (15.38%), breasts (11.81%) (Figure 2), face (10.16%) (Figure 3), back (1.56%) and abdomen (1.56%).

The modelling agent infiltration occurred between 1 month to 17 years (average 10.5 years). The first signs or symptoms (latency) occurred in 1 week to 17 years (average 5.8 years). Patients were treated at the wound care centre for an average of 1.5 years (1–6.5 years); however, 70% were lost to follow-up. The most common signs at the injection sites and distally were large indurated plaques (69.57%), erythema (65.11%), hyperpigmentation (65.11%), skin ulceration (16.09%), 'signs of infection' not otherwise specified (11.74%), purulent discharge (13.04%), scars and abscess formation (8.7% each), nodules and fistulae (4.35% each). Pain was present in 65.11% of the cases and malaise in 11.74%.

In 16 of the patients, characteristic findings of superficial and deep granulomatous dermatitis were observed along with a nodular infiltrate of histiocytes, lymphocytes, neutrophils, eosinophils and giant cells surrounding vacuoles of different sizes. Only three of the patients presented with granulomatous dermatitis alone; no vacuoles were observed in these patients. In patients where infection was suspected, swab or tissue cultures were performed. Atypical mycobacteria (*Mycobacterium fortuitum*) was documented in two of the patients. Extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* was present in two patients,



Figure 1 FMAR after injection of mineral oil in the buttocks.



Figure 2 FMAR associated with injection of silicone in the breasts.

one of the patients tested positive for *Pseudomonas aeruginosa*, and *Morganella morgagni* was detected in another patient.

Treatment and clinical course information was available for 11 patients. Half of the patients developed recurring infections over the course of their treatment. In these patients, systemic treatment was prescribed based on culture results. Treatment consisted of standard wound bed preparation techniques with advanced wound care dressings that provide moist healing. Debridement modalities included cold steel surgical, mechanical, maggot therapy and collagenase, and the modalities were selected according to the presence or absence of infection, pain and the amount of necrotic tissue to be debrided. In most patients, silver dressings were chosen; other dressings used were calcium alginate, polyhexanide-impregnated gauze, povidone-iodine and rapid capillary dressing. Negative pressure wound therapy (NPWT) was used in patients with large wounds or those with highly exudative wounds. Systemic anti-inflammatory treatment was given to one third of the patients and consisted of deflazacort, ibuprofen or a combination of both. Intra-lesional triamcinolone was applied in one patient.



Figure 3 Facial disfigurement caused by injection of silicone.

Two of the eleven patients had complete wound closure. One of the patients had localised FMAR to the face. Excision of the granulomatous area with autologous implants under the scars achieved closure with less residual scarring. The other had multiple infiltrated plaques but only a single hip wound that healed after NPWT and the application of grafts on the granulated tissue. Most other patients did consider their wounds improved to some extent.

Discussion

Clinical presentation

The age of presentation varies widely. The youngest patient in our series was only 18 years old. The majority of patients present were between the 30 and 40 years old (33,35–37). Clinical history depends on the nature and amount of the injected substance. The most commonly used foreign modelling agents are mineral oil, vegetable oil, guaiac oil and silicone. In Colombia and Brazil, cases of acrylates are commonly reported (8,30,32,33,35–38).

Most patients have continuous manifestations, but there may be cases where periods of spontaneous improvement alternate with severe exacerbations (37). Female patients have reported worsening symptoms during menstrual period (36). In male patients, worsening symptoms are associated with the use of hormonal steroid injection (36).

Local manifestations

As observed in our case series, the most commonly affected areas were buttocks and breasts; however, the modelling agent may be injected in almost any area, ranging from the face to the genitals (36–44). Given the fluidity of the materials commonly injected, migration by way of gravity or the lymphatics with infiltration of tissues far from the injected site are

very common causing the same type of lesions as it spreads (8,35,40). Furthermore, the material may migrate deeply, leading to partial or complete muscle involvement (40). Lymphadenopathy is common and it may be due to inflammation but also because of migration to the lymphatic nodules (40).

As seen in our patients, the most common local findings are inflammation (oedema, erythema, increased temperature), induration ranging from panniculitis-like to severe wood-hard fibrosis, scars (atrophic and/or hypertrophic), discoloration (hypo and/or hyperpigmentation), necrosis, ulceration, draining sinuses and exposure of the injected material (8,36,37,42). Some substances have been associated with specific signs; for example, polymethacrylate causes severe erythema and hyperpigmentation with hardening and deformity, while silicone is associated with inflammation and scarring (8). Dysfunctional scarring may be present and lead to contractures and loss of movement. The most commonly affected area in our patients was the buttocks. A likely explanation for this may be a very Latin American concept of beauty relating to wider hips and larger buttocks. Other frequently affected regions are the breasts, lower extremities and the face (35,36,44).

Systemic manifestations

Systemic manifestations depend on the amount and nature of the injected material, although even facial injections with very small amounts have also been associated with systemic syndrome (43). Patients may present with fever and malaise unrelated or related to infection as well as arthralgia, myalgia and Raynaud's phenomenon (36,42).

Systemic granulomatous reactions have been associated with FMAR, namely granulomatous hepatitis, renal failure, erosive arthritis and a systemic sclerosis-like collagen disease (35,37,45,46). One of the most feared and deadly complications is the pulmonary embolisation syndrome caused by the migration of particles of silicone through the circulation. The first report of the pulmonary repercussions of the injection of 1 litre of oil dates back to 1971 (47).

It may occur acutely as the silicone or foreign substance is injected inside a blood vessel, leading to sudden death, or it may present even after years of application, especially during surgical manipulation of abscesses (25). In the latter case, it causes progressive respiratory distress secondary to alveolar haemorrhage and inflammation (48). Another similar case showed silicone in all organs, including a layer forming on the top of precipitated post-mortem blood (10).

Diagnosis

Clinical criteria

The health care authorities in Mexico have proposed diagnostic criteria, which are summarised in Table 1. The authors of this review consider that not all FMAR cases will present with autoimmune disease manifestations or antibodies as previously described; therefore, these criteria should be considered with caution. Also, infection commonly co-exists in ulcerated FMAR.

Table 1 Diagnostic criteria for FMAR

- History of infiltration of a foreign modelling agent for cosmetic purposes
- Clinical manifestations of autoimmune disease
- Demonstration of autoimmune antibodies
- Histological evidence of chronic granulomatous inflammation with foreign body reaction
- Absence of infection or cancer
- Improvement with removal of the modelling agent or medical treatment of the autoimmune disease

Table 2 Simplified Alijotas-Reig criteria for diagnosis of FMAR

Major criteria

1. Exposure to external stimuli: biomaterials
2. Minimum latency of 1 month
3. Clinical involvement:
 - Local/regional: inflammatory nodules, skin oedema, induration, pseudo-abscesses, lymphadenopathy, panniculitis, morphea, sarcoid-like lesions, OR
 - Systemic: distant inflammatory nodules, arthritis, sicca or Sjögren's syndrome, myositis or muscle weakness, extended panniculitis, demyelinating neurological involvement OR
 - Evolution into organ or non-organ autoimmune disease
4. Foreign body-type biopsy of involved area or lymph nodes
5. Removal of inciting materials induces improvement
6. Compatible HLA (i.e. B8, DRB1, DR3, DQB1)

Minor criteria

- Recent history of triggering factors preceding onset of clinical manifestations (i.e. infection, trauma, etc.)
- Large, de novo livedo reticularis and/or hand erythema at the onset of clinical manifestations
- Presence of any auto-antibody and/or hypergammaglobulinemia and/or increased ACE and/or LDH and/or hypocomplementemia.

Recently suggested diagnostic criteria for autoimmune-inflammatory syndrome induced by adjuvants include only objective clinical and laboratory data (15). These criteria apply to many diseases and syndromes mediated by haptens. A simplification of the criteria limited to FMAR is presented in Table 2.

Torres-Gomez *et al.* suggest an instrument to evaluate and stage the damage caused by FMAR (39). It consists of seven parameters to be evaluated, namely (i) amount of infiltrated modelling agent, (ii) number of infiltrated areas, (iii) type of substance used, (iv) symptoms, (v) signs, (vi) laboratory studies and (vii) magnetic resonance imaging (MRI) findings. These results give a score that divides patients into four stages (Table 3). This first attempt at providing prognosis based on the severity of the disease is limited by the fact that some of the criteria are poorly supported by evidence. Moreover, Torres-Gomez *et al.* failed to define each criterion with precision. Lastly, MRI availability may be limited in most of Latin America.

A classification for mammary FMAR was also developed by Priego-Blancas (44). In 56 women with mammary FMAR, the authors were able to define six stages (Table 4).

Table 3 Instrument to score the severity of FMAR as suggested by Torres-Gomez *et al.* (39)

					Score
Amount infiltrated	1	2	3	4	
	Less than 200 ml	200–500 ml	500–1000 ml	More than 1000 ml	
Number of infiltrated areas	1	2	3		
	One area only	Two–three infiltrated areas	More than three areas		
Type of infiltrated substance*	1	2	3	4	
	Silicone	Biopolymers or methacrylates	Oils	Mixtures	
Symptoms	1	1	1	1	
	Local infiltration	Fever and malaise	Arthralgias, myalgias or autoimmune disease	Pneumopathies	
Signs	1	1	1	1	
	Nodules	Substance migration	Hyperpigmentation and sclerosis	Ulcerations and infection	
Laboratory studies	0	1	1	1	1
	Normal	Leukopenia	Elevated CRP	Elevated ESR	Multiple organ failure
Affected tissues as per MRI	1	1	1		
	Skin and subcutaneous tissue	Muscular involvement	Deep organ involvement		
					Total

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FMAR, foreign modelling agent reactions; MRI, magnetic resonance imaging.

*The type of infiltrated substance must be known. Otherwise magnetic resonance spectrometry in a biopsy sample is recommended.

Table 4 A classification for mammary FMAR

Stage 0	Asymptomatic or symptomatic infiltration without palpable masses
Stage 1	Single tumour with normal skin or just discrete discoloration; no affection to nipple, muscle or ribs
Stage 2a	Single or multiple tumours with normal nipple or retracted but without anatomical compromise
Stage 2b	Same as 2a but with muscular affection
Stage 3	Single or multiple tumours with skin and nipple infiltration with sclerosis, atrophy or ulceration
Stage 4	General affection of the breast including skin, nipple, muscle and ribs
Stage 5	Same as stage 4 but with severe systemic compromise that make them poor surgical candidates

According to this classification patients are treated with diverse modalities, including laboratory and imaging studies.

Laboratory studies

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may be elevated. A complete blood count (CBC) may show leukocytosis or leukopenia, lymphopenia, eosinophilia or thrombocytopenia. Specific measurements of silicone in blood have also been reported to be elevated (8).

In immunological tests using rheumatoid factor (RF), immunoglobulins or auto-antibodies (antinuclear antibodies [ANA], anti-DNA antibodies, anticardiolipin antibodies or

antineutrophil cytoplasm antibodies [ANCA]) and tumour necrosis factor (TNF)- α , findings may be elevated as well (8).

Whenever skin integrity is compromised, cultures may be taken for bacteria, mycobacteria and fungi.

Imaging studies

Imaging studies are extremely valuable in the diagnosis of FMAR and its complications. A chest x-ray may show the presence of pleuritis, pneumonitis and/or fibrosis (37). The imaging study that provides the most valuable information is MRI. The location, amount and extension of the damage caused by the modelling agent can be visualised, as well as the presence of inflammatory activity (8,36,37,41,42,44,46,47,49,50). Several infiltration patterns have also been described, namely mixed, globular, linear or pseudonodular (40). Most commonly, the depth of the affection reaches down to the muscles (39).

In a recent study of tissue samples of 18 patients, MRI spectrometry in biopsy samples (Figure 4) was able to specify the nature of the modelling agent injected: 35% was cooking oil (triglycerides), 40% mineral oil (petrolatum or hydrocarbons), 15% silicone and 15% a mixture of the first two (38,51).

When MRI is not an option, ultrasound may be used to evaluate inflammation, measure the affected area and estimate the amount of modelling agent injected (8,49). The main findings are increased density and echogenicity of the subcutaneous tissue (44).

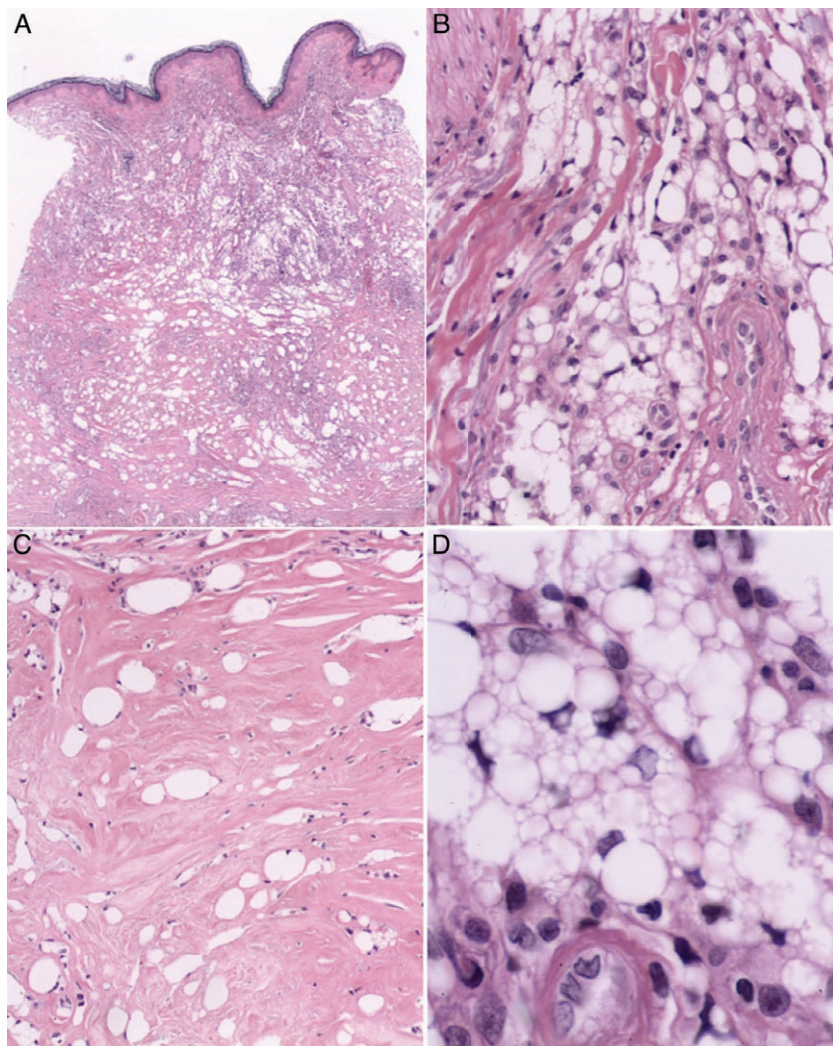


Figure 4 (A) Skin biopsy of an infiltrated plaque (H and E 2x), showing a superficial and deep infiltrate of histiocytes and empty vacuoles interspersed between thickened collagen bundles. Note the absence of adnexal structures. (B) (H and E 10x) Dermal infiltrate of vacuolated histiocytes. Characteristically, vacuoles are of many different sizes. (C) (H and E 5x) Subcutaneous tissue is replaced by hypocellular hyalinised collagen admixed with empty vacuoles. (D) (H and E 40x) High-power view of foamy histiocytes with numerous vacuoles within their cytoplasm.

Histological findings

Tissue samples are recommended to confirm and document the diagnosis (37). The main feature in the histology of FMAR is granulomatous chronic inflammation with a foreign body reaction, where there are foamy histiocytes or multinucleated giant cells with phagocytised foreign material. Commonly, empty vacuoles are formed interspersed within the inflammatory infiltrate. Special stains, such as Sudan IV, Nile blue or osmic acid, may further characterise these vacuoles (10,41–44,49–52) (Figure 4).

The epidermis may or may not be affected depending on the presence of ulceration. Because FMAR is deeply injected, both the subcutaneous fat and the dermis are commonly affected. The inflammatory infiltrate is mixed with mainly histiocytes and lymphocytes, but neutrophils and eosinophils may be present. Different degrees of fibrotic areas may appear interspersed with the granulomatous reaction (49).

Differential diagnosis

When the history of infiltration is not clear or present, the clinician should rule out other forms of panniculitis or vasculitis. In the presence of sclerotic atrophic plaques, localised

scleroderma, morphea or even systemic sclerosis should be investigated. Breast nodules should be biopsied in all cases to exclude cancerous lesions. Cutaneous xanthomas or xanthogranulomas may look like small plaques formed after superficial injection of silicone, especially in the face. Atypical mycobacteriosis may look like some of these lesions, but may also co-exist with FMAR (41).

Treatment

The treatment of FMAR is complex and requires a multidisciplinary approach. In mild cases, proper wound care may be the only necessary treatment, but in more severe cases, surgical procedures and systemic therapy may be necessary (35). The team necessary to aid these patients may include professionals in mental health, dermatology, general surgery, plastic surgery, rheumatology, infectious diseases and rehabilitation medicine (35). Criteria associated with poor response are persistent elevation of acute inflammation markers, poor response to deflazacort, the presence of autoimmunity, elevated levels of silicone in blood and high TNF- α (8). Most patients with FMAR will develop chronic relapses, but once again, this will depend on the type and amount of modelling agent injected. Given the long

duration of treatment, patients with FMAR become quickly frustrated; thus, loss to follow-up is very common.

Local: surgery and wound care

Surgical modalities include incision and drainage of both hot and cold abscesses, surgical debridement with removal of infiltrated areas and reconstructive procedures (35,42).

In a series of five patients with penile paraffinoma, surgical removal and reconstructive procedures led to improvement without penile shortening (53). Other cases with surgical resection in male genitalia have been reported (24,54). A localised lesion on the knee area was also successfully treated with resection (41). As large amounts of injected modelling agent tend to mix with healthy tissue, surgical removal can be difficult (31,34,37). Surgical liposuction and ultrasound liposuction have been used (8). Haddad *et al.* reported on six patients who underwent transversus rectus abdominis muscularis (TRAM) flap reconstruction after the removal of the foreign modelling agent, with acceptable results (55). A patient who was injected in both breasts with mineral oil had recurring fistulas and inflammation that resolved after bilateral Patey-type mastectomy and the same TRAM reconstruction (52).

In a series of 110 patients, using the Torres-Gomez staging system, none of the patients in stage 1 required surgery and they responded only to pharmacological treatment. In more than 90% of the patients in stages 2 and 3, surgical resection resulted in improvement. However, two of the patients in stage 4 died of multiple organ failure (39).

Priego-Blancas proposes that stage 0 be treated with observation and anti-inflammatories only (systemic steroids and/or methotrexate and/or colchicine for at least 6 months) (44). For stage 1, resection of the modelling agent and direct closure is recommended. For stage 2a, Priego-Blancas suggests subcutaneous mastectomy with or without implants and for 2b, depending on the muscular affection, besides the implant, a latissimus dorsi flap. For stage 3, simple mastectomy and TRAM reconstruction or free cutaneous flap should be considered. For stage 4, simple mastectomy and reconstruction with free latissimus dorsi flap are recommended. Finally for stage 5, given the poor prognosis and general medical condition, only medical treatment should be offered until surgery can be performed.

Dermabrasion was used to treat silicone granuloma in a female patient who had received silicone injections on her hips for cosmetic purposes. She developed oozing granulomas on her legs 10 years after the treatment. This patient was reported as having severe pain after discharge and developing healthy granulation tissue, yet only areas of epithelialisation were achieved; therefore, until further reports show better results, dermabrasion does not seem to solve these granulomas (42).

Local treatments of all kinds have been reported. Penile paraffinoma showed improvement after topical application of potassium permanganate soaks (47). Conservative treatment following the principles of wound bed preparation (i.e. tissue debridement, infection/inflammation control, moisture balance using proper dressings) may achieve good results.

Systemic

Systemic steroids and immunosuppression may be necessary when systemic inflammation is present with re-evaluation every 4 months (35,42). In a case series of 75 patients, the authors suggest a treatment protocol with the initial administration of deflazacort 11–15 mg during the first 30 to 45 days. If no response is recorded, then the addition of azathioprine, colchicine, thalidomide, hydroxychloroquine or mycophenolate should be considered for 3 months. After 3 months, if the disease is still active, the treatment was switched to cyclophosphamide or etanercept. Following this scheme, the authors report that 75% of the patients responded to the combination of deflazacort and colchicine. Unfortunately upon discontinuation of therapy, inflammation recurred in 91% of the patients after 5 months (8).

The use of tetracyclines, both as antibiotic and anti-inflammatory, was advocated as efficacious in a case report of oil injections in the buttocks of a patient unresponsive to cephalexin and prednisone (56).

Complications

Complications derived from FMAR can be described as local and systemic. Locally, complications will relate to the inflammation and scarring caused by the agent and the anatomic region. Paraffinomas of the penis lead to erectile dysfunction and acute urinary retention (40,45,46,50).

Almost 7% of patients will also be scarred as a result of treatment (8). Squamous cell carcinoma may present on the chronic inflammatory ulcers and sinuses that resulted from FMAR (33).

Systemic complications may lead to granulomatous hepatitis, pneumonitis, systemic embolism in almost any organ or system, acute pulmonary oedema and autoimmune disease (33,36). Whether silicone and other substances are associated with connective tissue diseases remains controversial. Despite the increased number of cases reported in the literature, no association has been convincingly established (57). In a case series by Cabral, 71% of patients had positive antinuclear antibodies (1).

Conclusion

FMAR has been defined as any clinical manifestation, local or systemic, histopathological, presenting after parenteral administration of non-biodegradable substances meant to model the body (37,39). Although anyone can present with FMAR, the largest series have reported that it is by far most common in women and homosexual and transsexual men (31,39). Middle classes (87%) are most commonly affected (36). In the MGH, the reported incidence of FMAR is 5 to 10 new patients per week (33).

FMAR is caused by injection of foreign substances into the soft tissues in order to alter the body contours. Cosmeticians and non-medically trained personnel inject most of the patients (70%), but physicians and other health-related personnel have also been implicated (37). Many substances have been implicated as aetiological agents. The most commonly injected are

oils and greases (both mineral and vegetable), silicones, acrylates, vitamins, bee's wax and polyglycolic acid, but many others have also been reported (33,37,42). Industrial-grade mineral oil usually causes a more severe disease (40). The risk of developing a siliconoma increases with the amount injected (39).

The pathophysiology of FMAR depends on the agent and amount infiltrated. Studies in mice and other animals have shown that there is transfer of silicone molecules from macrophages to lymphocytes through cytoplasmic bridges. While studies examining the effect of varying amounts of agent are lacking, it is assumed that the response can be more intense with an increasing molecular size of the agent (38,45,46,50).

Many terms and synonyms have been used to describe FMAR. The first terms proposed related mostly to the substance being infiltrated, such as paraffinoma and siliconoma, which made it difficult for health care professionals to classify patients when the agent did not fall in one of the predefined categories (e.g. metamethylmethacrylate) or when the real nature of the injected agent was not known (3,10). Later, on the basis of histological images, the foreign agent reactions were termed sclerosing lipogranuloma; however, this term failed to relate it to the injection of modelling agents (39). The term human adjuvant disease or autoimmune inflammatory syndrome induced by adjuvants was later introduced in the medical literature to describe the systemic reaction caused by the infiltration of foreign materials (12,15). These terms are widely used to include a series of diseases that range from FMAR to Gulf War Syndrome, vaccine reactions or even sick building syndrome, making it a broad term to describe a neo-haptens-mediated group of ailments (15). In Latin America, the term iatrogenic allogeneic is used (34). This term is inappropriate because most of the cases of FMAR are caused by unlicensed cosmeticians and not by medical practitioners. Moreover, the term allogeneic refers to tissues or cells from a different organism of the same species, which does not accurately describe the cause of the reactions.

Previously proposed terminology has caused confusion in the medical literature, making it very difficult for non-specialists or health care professionals from countries with a low incidence of the problem to understand its relevance. FMAR has implications that go beyond the mere immunological response, has a psychological impact and carries an increased risk for morbidity and mortality. Therefore, the term we propose, foreign modelling agent reaction (FMAR), is more descriptive of this syndrome that has reached epidemic proportions in Latin America and Asia.

Management of FMAR requires a multidisciplinary and specialised approach that applies proper classification and evaluation of the patients to achieve better outcomes and avoid unnecessary morbidity and mortality. In countries with high prevalence of FMAR, public policy should be implemented to educate the general population. As FMAR is destructive in nature and has poor prognosis and high morbidity and mortality rates, the most important focus should be on prevention. In 1972, Fernando Ortiz-Monasterio concluded in a series of 186 patients that the treatment was so frustrating and unsatisfactory that strict law enforcement and government involvement in prevention should be more aggressive (12).

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