

Illicit massive silicone injections always induce chronic and definitive silicone blood diffusion with dermatologic complications

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Abstract

Male-to-female transgender (MtF TG) individuals often report using illegal subcutaneous silicone injections for body feminisation. It leads to silicone dissemination and various dermatologic complications.

We report the long-term complications of these feminisation procedures with blood smear examination and dermatologic examination.

Between July 2015 and December 2015, 77 MtF TG consulting at Bichat Hospital (Paris, France) were included in this cross-sectional study. Blood smear examinations were performed by a trained haematologist to quantify the presence of silicone vacuoles in monocytes.

All patients reported a history of massive amounts of silicone injections (mean 4 L, range 0.5–15 L). Most patients were South American (75/77, 97%). Fifty-nine (59/75, 79%) were HIV-seropositive, mostly with undetectable HIV RNA plasma levels (46/58, 80%). Clinical examinations reported dermatologic complications for all patients: lymphatic or subcutaneous migration of silicone (59%), inflammation (50%), varicose veins (39%), post-inflammatory pigmentation (20%), infection (14%) and abscesses (4%). Blood smear examination showed intracytoplasmic vacuoles containing silicone in monocytes in all patients.

We did not chemically prove the silicone nature of the vacuoles. The design of this study does not allow evaluation of short-term complications that should not be minimized.

Illicit massive silicone injections always induced chronic and definitive silicone blood diffusion with dermatologic complications. This study highlights the dangers and the inefficiency of clandestine esthetic surgery. There is a need for targeted information campaigns with transgender populations about silicone injections. Otherwise, these practices may persist.

Abbreviations: ALCL = anaplastic large cell lymphoma, CPK = creatine phosphokinase, CRP = C reactive protein, EDTA = ethylene-diamine-tetra-acetic acid, FDA = Food and Drug Administration, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = human immunodeficiency virus, MGG = May–Grünwald–Giemsa, MtF = male to female, RNA = ribonucleic acid, TG = transgender.

Keywords: dermatology, macrophages, phagocytosable silicone, silicone injection, transgender

1. Introduction

The term transgender (TG) refers to persons whose gender identity does not match with their assigned sex at birth. Male-to-female (MtF) TG individuals identify as women but were born

with male anatomy. The feminisation process varies from cross-dressing and hormone replacement therapy to surgical procedures, ranging from facial feminisation surgery and breast prosthesis to sex reassignment surgery. An illegal and less expensive alternative for body sculpting is the use of massive subcutaneous silicone fluid injections. Unqualified persons in nonmedical facilities frequently perform this in many Latin American countries. Silicone injections may lead to acute life-threatening complications such as systemic silicone embolism and acute pneumonitis and later chronic dermatologic complications.^[1,2] Side effects caused by these injections are often ignored by patients and underdiagnosed by doctors leading to the persistence of these dangerous practices.

During acute complications, circulating silicone has been identified in blood vessels and many distant organs, as silicone vacuoles in capillaries or within alveolar macrophages.^[3–6] Chronic silicone deposits and inflammatory reactions may be observed in various distant organs suggesting chronic silicone migration.^[7] Few studies have been published reporting chronic systemic blood diffusion of illicit silicone or descriptions of associated adverse skin effects.

The aim of this study was to provide evidence pertaining to the presence and chronic persistence of silicone in circulating monocytes in MtF TG patients. Secondary objectives were to describe the dermatologic complications in this TG population.

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2. Methods

All MtF TG patients over 18 years old with a history of cosmetic silicone injections who consulted at Bichat Hospital (Paris, France) from June 2015 to December 2015 were included in this cross-sectional study after providing informed consent. Patients under guardianship or those unable to communicate were excluded (flowchart, Fig. 1). The local ethics committee approved the study protocol.

Outpatients were included during their visit in the Infectious Diseases or Dermatology Department. For each patient, one of the 3 investigators (CB, FM, and FB) collected the following data: age, human immunodeficiency virus (HIV) status, current or former co-infections [tuberculosis, hepatitis B virus (HBV), hepatitis C virus (HCV), syphilis], hormone replacement therapy, silicone breast prostheses, and silicone injection characteristics (date, volume, and location). Dermatologic examination evaluated the presence and type of local complications: lymphatic migration to groin lymph nodes, varicose veins of usual or unusual location, infiltration of the inner thighs or of the sacrum, visible or palpable inflammation (plaques, nodules called siliconomas, and swelling-like symptoms), infection (cellulitis, erysipelas, and necrotising fasciitis) and/or abscesses and post-inflammatory pigmentation. Blood samples were collected for blood smears, measures of inflammatory markers [C-reactive protein (CRP) and ferritin], HIV test control, HIV-RNA level (copies/mL) and CD4 lymphocyte cell count level if needed (values older than 6 months). Smears from ethylene-diamine-tetra-acetic acid (EDTA)-anticoagulated blood were analyzed with light microscopy by a trained hematologist (VA) without any information on clinical and biological data. Twenty-five monocytes per blood smear were studied. May–Grünwald–Giemsa (MGG)-stained blood smears were carefully examined for the presence or absence of unusual optically empty intracytoplasmic vacuoles in the monocytes. The percentage and shape of monocytes with intracytoplasmic vacuoles were recorded as well as the number, size and location of the vacuoles. Vacuoles were classified into 2 groups: the first group represented vacuoles of size $<2 \mu\text{m}$ in diameter (<2 Howell–Jolly bodies in

diameter) and the second group consisted of giant vacuoles defined by a size equal to or above 2 microns in diameter. Quantification of silicone presence was based on the number of vacuoles per monocytes and the number of giant vacuoles among all vacuoles.

For all included patients, clinical and cytological characteristics were described by their mean and standard deviation (for quantitative variables) or their count and proportions (for categorical variables). We categorized dermatologic complications into 3 groups: C1 for silicone migration or varicose veins, C2 for inflammation or postinflammatory pigmentation, and C3 for infection or abscesses. Comparisons were based on local complication groups using Wilcoxon tests (for quantitative variables) and Fisher exact tests (for categorical variables). The threshold of 0.05 was used for the significance. All analyses were performed using R software 3.2 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Description of the population

The study included 77 MtF TG patients. Seventy-five patients (75/77, 97%) were of South American origin. Fifty-nine patients (59/75, 79%) were HIV-seropositive. All HIV-seropositive MtF TG patients were receiving antiretroviral therapy. HIV-RNA levels were undetectable (<20 copies/mL) in 80% of cases (46/58) and mean CD4 lymphocyte count was $650/\text{mm}^3 \pm 268$. HIV infected patients had a more frequent history of syphilis compared to HIV-seronegative patients (65% vs. 33%, $P=.04$). There was no difference between HIV-seropositive and seronegative subgroups for other conditions, namely tuberculosis, HBV, HCV, hormone replacement therapy, volume of injected silicone, number of years from silicone injection, biological inflammatory syndrome prevalence and dermatologic complications. All patients had a history of silicone injections in the hips and buttocks. Some of them had also received injections in other sites: thighs, cheeks, forehead, and chin. Three patients had genital reassignment surgery. Most of the injections were performed

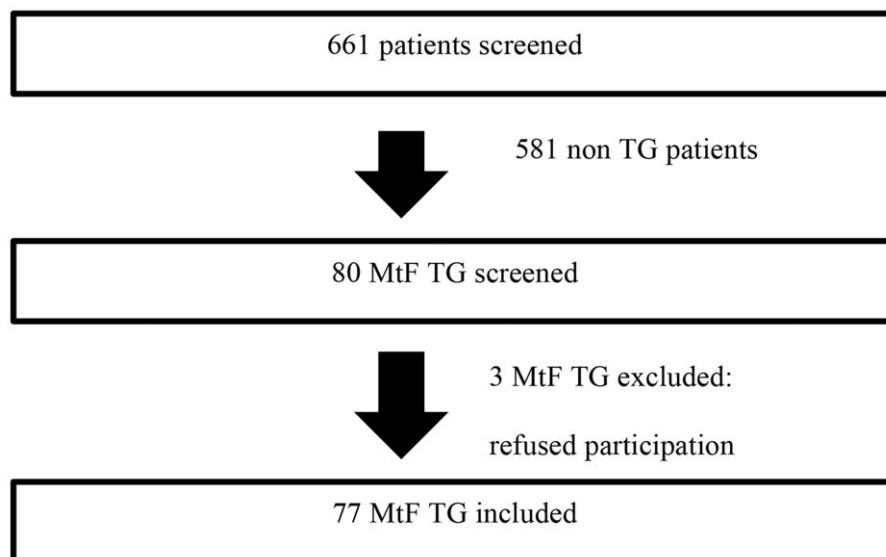


Figure 1. Flow diagram. Flow diagram for study sample size and selection of study participants. MtF= male to female, TG=transgender.

Table 1
Patients' characteristics.

Characteristics	HIV- (n=16)	HIV + (n=59)	P-value	Total (n=77)	Number of missing values
Age, years	34.7 ± 7.1	42.0 ± 9.3	.002	40.4 ± 9.3 (20–68)	5
HBV positivity	3 (19%)	24 (51%)	.145	27 (36%)	2
HCV positivity	0 (0%)	5 (9%)	.579	5 (7%)	3
History of tuberculosis	3 (19%)	25 (45%)	.083	28 (39%)	5
History of syphilis	5 (33%)	35 (65%)	.04	40 (58%)	8
Hormone intake	8 (57%)	20 (51%)	.763	28 (53%)	24
Silicone breast prosthesis	14 (93%)	34 (76%)	.262	48 (80%)	17
CRP, mg/L	3.42 ± 10.64	3.60 ± 9.55	.4	3.56 ± 9.68 (0–57)	18
Ferritin, ng/mL	103.3 ± 41.1	110.2 ± 87.4	.457	108.3 ± 76.8 (17–427)	31
Quantity of injected silicone, L	4.43 ± 3.52	3.86 ± 2.48	.745	4.03 ± 2.79 (0.5–15)	25
Years from injection	13.56 ± 6.62	16.78 ± 7.08	.129	15.79 ± 7.04 (2–36)	25
Illegal injection	14 (93%)	36 (92%)	1	50 (93%)	23

Data are presented as number (%) or mean ± standard deviation (interquartile range—IQR).
CRP=C-reactive protein, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV +=human immunodeficiency virus seropositive, HIV- =human immunodeficiency virus seronegative.

unprofessionally (50/54, 93%) with nonmedical grade silicone fluids (usually industrial lubricants). Mean time between injections and inclusion in the study was 16 years (range 2–36 years). The use of massive quantities of silicone fluids was reported (mean 4 L, range 0.5–15 L). Forty-eight patients had silicone breast prostheses (48/60, 80%) (Table 1).

3.2. Description of dermatologic complications

Dermatologic complications were observed in all patients (Fig. 2). The following order of frequency was observed: lymphatic or subcutaneous migration of silicone (33/56, 59%), inflammation (28/56, 50%), varicose veins (22/56, 39%), postinflammatory pigmentation (11/55, 20%), infection (8/56, 14%), and abscesses (2/55, 4%). We noted 2 cases of localized cutis laxa with skin atrophy and frequently observed oedema around the ankles and dorsum of the feet with frequent athlete’s foot. Dermatologic complications belonged to C1, C2, and C3 groups in 70%, 56% and 14%, respectively.

The presence of complications was not associated with patients’ age but with the number of years after silicone injections. The median time since silicone injections was 17 years for patients with silicone migration or varicose veins versus 13 years for other patients (P=.025). There was a similar tendency with postinflammatory pigmentation or inflammation (P=.067). Silicone migration or varicose veins were also associated with lower mean CD4 count (580CD4/mm³ vs 770 CD4/mm³, P=.036). Infectious complications were less frequent in MtF TG patients who had silicone breast prostheses (37% vs 85%, P=.01). No correlation was found between mean CD4 count and other complications, in particular infectious ones.

3.3. Blood smears

All patients had intracytoplasmic vacuoles in monocytes (Fig. 3). Vacuoles were present in the majority of studied monocytes (mean 94%, range 48%–100%), with an average number of 9 vacuoles per monocyte (range 3–14 vacuoles). The mean

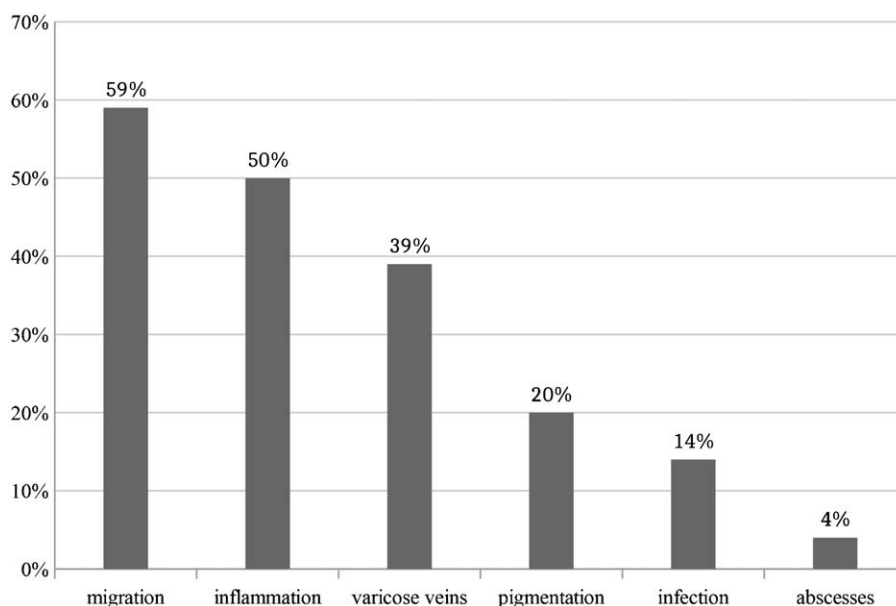


Figure 2. Chronic dermatologic complications in MtF TG patients (percentages). MtF=male to female, TG=transgender.



Figure 3. Buttocks silicone injection. Silicone injection in buttocks in a TG resulting in pigmentation, varicose veins and siliconomas. TG=transgender.

proportion of monocytes with giant vacuoles was 27% (range 4%–48%). Most intracytoplasmic vacuoles clustered near nuclei. Monocytes with vacuoles had regular plasma membranes. Compared to HIV-seropositive patients, HIV-seronegative patients had a higher proportion of vacuolated monocytes (99% vs 92%, $P=.002$) and a higher mean number of vacuoles per monocyte (10 vs 8, $P=.035$).

No correlation was shown between vacuole counts and the following parameters: volume of injected silicone, time after first silicone injection, CD4 lymphocyte count, and inflammatory biological parameters.

4. Discussion

In France, health authorities estimate the prevalence of TG between 1/10,000 to 1/50,000 people, while in North America 0.6% of the population identifies themselves as TG.^[8,9] Worldwide, MtF TG individuals have a very high risk of HIV and sexually transmitted infections (STIs) with an HIV seroprevalence of about 20%, 50 times higher than in the general population.^[10] As observed in the literature our patients had a high infectious risk of HIV, STIs and tuberculosis, and good observance and adherence to antiretroviral therapy.^[11–13]

This study illustrates the unavoidable dermatologic complications and the definitive silicone blood diffusion after illicit subcutaneous silicone injections. All MtF TG patients had intracytoplasmic empty vacuoles in circulating monocytes (Fig. 4). These vacuolated monocytes had smooth plasma membranes, not irregular as seen in activated monocytes. There was no relevant association between clinical or biological criteria that could explain the variations of vacuole numbers per monocyte. No statistical association was evidenced between the amount of injected silicone or the time distance since the injection and the vacuoles number. The vacuole number may depend on the type, nature, and density of injected silicone, which is unknown in our cases considering its illicit and nonmedical origin. Dermatologic complications were constant and persistent. We suggest a classification of these complications, based on the inflammatory component that can be used by any dermatologist (Table 2).

Silicone has been mainly used in cosmetology and was initially considered as an inert component and minimally antigenic filler. Despite its prohibition its use persists particularly among the TG population for body shaping.^[14] In this context, industrial silicone is subcutaneously injected. These illegal and massive silicone injections can lead to silicone embolism syndrome, similar to fat embolism syndrome, and acute pneumonitis within the first few hours. The systemic embolization mechanism is

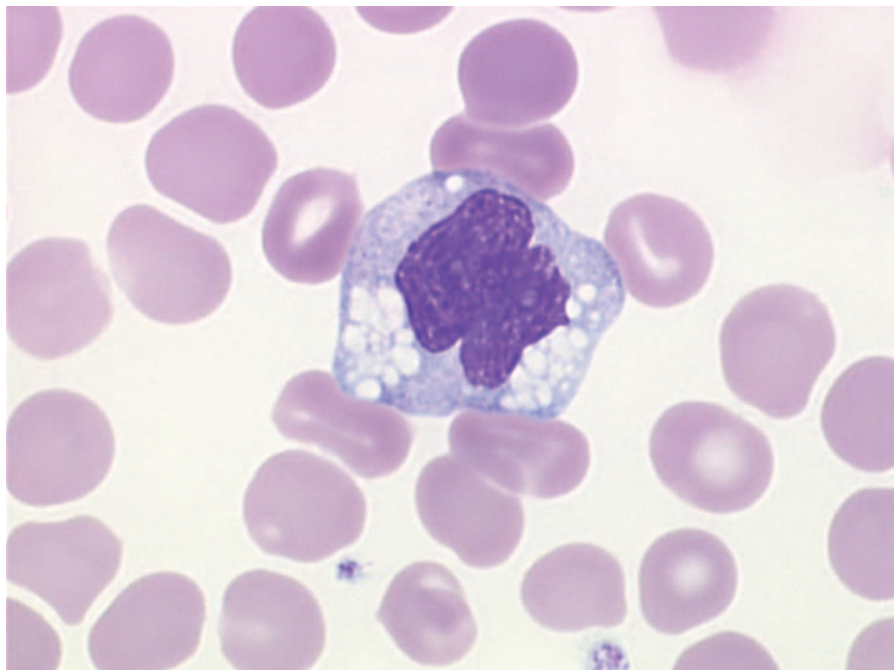


Figure 4. Circulating monocyte. Multiple intracytoplasmic vacuoles (May–Grunwald–Giemsa (MGG)-stained blood smears, original magnification $\times 100$). MGG=May–Grunwald–Giemsa.

Table 2
Classification of silicone-induced dermatologic complications.

	Inflammatory	Noninflammatory
Early complications < 1 week	Oedema Erythema Soft tissue infections: cellulitis, necrotising fasciitis	Deep venous thrombosis Haemorrhage Necrosis
Late complications > 1 year	Acute episodes: Inflammatory outbreak Mastitis Soft tissue infections: cellulitis, abscess, necrotising fasciitis Mycobacterial abscess Fistulas Subacute/chronic complications: Siliconomas Chronic wounds Postinflammatory lesions: Pigmentation Induration Atrophy Cutis laxa	Migration Varicose veins Oedema

unknown but could result from local tissue damage allowing silicone migration into the vascular circulation, direct intravascular injections, or phagocytosis by histiocytes and generalized disposition in the reticuloendothelial system.^[1,4] During early complications, silicone has been identified as siloxane elements in blood and as silicone vacuoles in capillaries or within alveolar macrophages. These vacuoles are prominent pleiomorphic cytoplasmic inclusions described at electron microscopy.^[4,3] The peculiar cytological feature described in these macrophages disclosed abnormalities similar to those found in our patients' monocytes. Only animal studies have reported the same silicone presumed vacuoles in peripheral blood neutrophils and mono-

cytes of mice and baboons after the subcutaneous or intraperitoneal administration of silicone fluid.^[15]

Latent silicone pneumonitis may be observed in patients who develop local inflammatory reaction at injections sites. Silicone deposits and inflammatory reactions are observed in skin biopsies and various distant organs samples (e.g., lungs, brain, heart, kidney, liver, spleen, and pancreas), confirming silicone migration.^[1,6,4] Histological processes are described as "swiss cheese" with numerous vacuoles present in multinucleated giant cells and macrophages cytoplasm, interstitium, and cystic spaces. The optically empty vacuoles might simulate adipocytes but are smaller, refractile, and colourless. They are associated with dilated capillaries and granulomatous foreign body reactions called siliconomas (Fig. 5).^[5] It may be difficult to distinguish these granulomas from infectious granulomas of atypical mycobacteriosis or skin tuberculosis. Five cases of cutaneous tuberculosis diagnosed on gluteal abscesses in HIV-positive Brazilian TG patients with previous tuberculosis were recently reported.^[16] We reported a similar complication with a multidrug resistant tuberculosis strain in gluteal abscesses in an HIV-seropositive TG.^[17]

Massive injections of nonmedical grade silicone induce dermatologic complications, whose diagnoses and treatments are not standardized. Early complications appear within days of injection, while later complications are described in subsequent years.^[18] The most common dermatologic complications range from localized inflammation to extensive siliconomas or ulcerations.^[19] In our study silicone migration was the most frequent complication (59%) and may be mechanically explained, as it follows gravity and deposits in groin and along the legs. This favors leg oedema and increases the risk of deep venous thrombosis and infection. Inflammation can occur spontaneously or after a traumatism, and may lead to post inflammatory pigmentation. It may also depend on the purity degree of injected silicone, which was unknown as most of the patients received nonmedical grade silicone. Varicose veins may result from

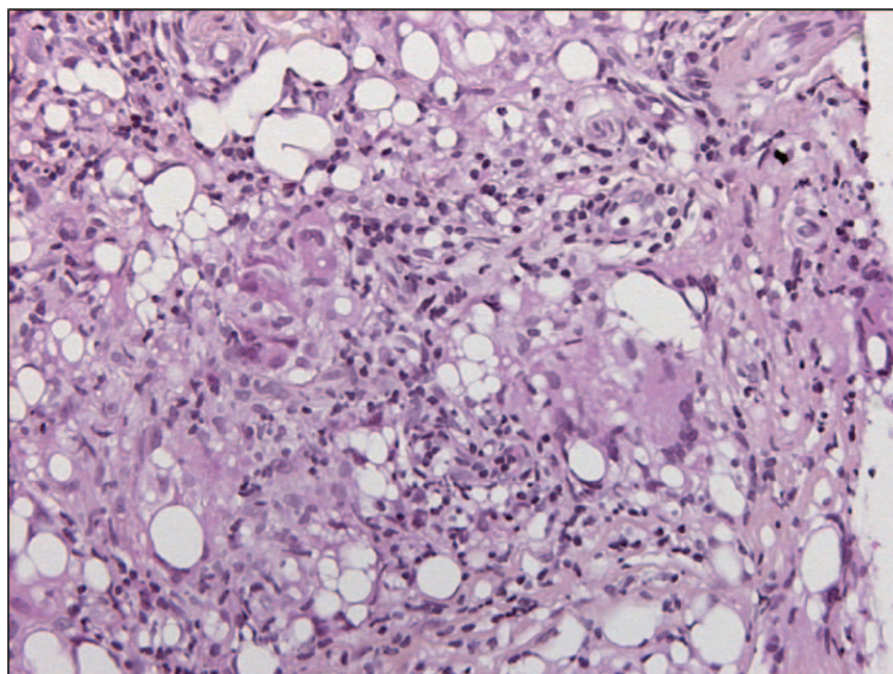


Figure 5. Skin histology. Multinucleate giant cells phagocytosing vacuoles of silicone (original magnification ×50 and ×200).

lymphatic and superficial veins obstruction by silicone. Infection and abscesses develop after minor skin wounds. No correlation between HIV-seropositivity or immunodepression level (CD4 count, viral load) and infectious complications was found. Patients with breast silicone prostheses were less likely to have infectious complications (7% vs 42%). An explanation could be the higher socio-professional groups of TG patients who could afford real breast prostheses and might have had easier access to care.

The treatment of dermatologic complications is first based on prevention measures. Venous Doppler ultrasound may rule out associated deep venous thrombosis. Chronic venous complications are treated with adapted venous compression. All minor wounds (i.e., athlete's foot) and common soft tissue infections must be treated to reduce the risk of severe infections on chronic leg oedema. In some cases, inflammatory outbreaks are controlled with cyclins or colchicine for a few weeks. Infectious episodes are treated with empirical antibiotherapy (beta lactams, pristinamycin). Surgical treatment must be reserved for necrotising fasciitis. In other cases, it can lead to major disrepair and prolonged healing. Leonardi et al^[20] proposed a surgical treatment algorithm based on a literature review of treatment options and their own experience. Clinicians should be aware that it is not possible to take away silicone deposits. They should also inform the patients that self-treatment, especially corticoid use, is deleterious and highly prohibited.

The limitations of this study are as follows. It was a monocentric and transversal study with a recruitment bias as a majority of patients were HIV seropositive. They were mainly attending to the Infectious Diseases Department where more than 200 HIV-seropositive MtF TG patients are currently treated. The prevalence of HIV infection in this study is also probably overestimated as the French system offers free access to care for HIV infected patients. Missing values were linked to incomplete questionnaires or technical issues for the missing blood smears. We did not chemically prove the silicone nature of the vacuoles but found strong cytological similarities with bronchoalveolar lavage fluid content and descriptions from animal studies supporting this hypothesis. Even if there was no control group of patients with no history of silicone injections, such specific cytological features are not observed in routine blood smear observations. We could not explore the link between monocytes with intracytoplasmic vacuoles and silicone breast prostheses because of a lack of control subjects. In fact, 80% of the population had prostheses, while all had monocytes with intracytoplasmic vacuoles.

We did not study the occurrence of autoimmune disorders related to silicone injection (systemic sclerosis, rheumatoid arthritis, Still's disease, systemic lupus erythematosus, and fibromyalgia). These complications were described in 2011 by Shoenfeld and named as siliconosis under a common syndrome entitled ASIA (autoimmune/auto-inflammatory syndrome induced by adjuvants).^[21] Silicone implication remains controversial.^[22] Regarding breast prostheses, it is hypothesized that silicone uptake by macrophages results in cellular activation and secretion of inflammatory mediators, resulting in chronic inflammation, fibroblast proliferation and collagen deposition around the implant. Others have suggested the role of low-grade bacterial contamination of the implant surface, rather than the body's reaction to silicone.^[23] Cases of anaplastic large cell lymphoma (ALCL), kinase-1-negative are emerging and could also be triggered by silicone leakage from the prosthesis.^[24]

5. Conclusion

Illicit massive silicone injections induce chronic silicone blood diffusion inside circulating monocytes as well as severe dermatologic complications leading to major disfigurement. These complications lead to unaesthetic lesions that definitely alter the external appearance that is essential in the affirmation process of TG identity. Information campaigns to prevent these practices are fundamental. Clinicians should be aware of undeclared silicone injections and seek that information at first consultation.

The immunological consequences of persistent silicone diffusion and chronic local inflammation are still unknown. The next step is to assert the presence of silicone in the intramonocytic vacuoles and to characterize the monocyte activation profile and possible functional consequences. This might help to understand the link between monocytic silicone saturation and immunological or oncogenic issues.

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