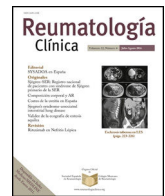




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Brief report

Autoimmune and malignant diseases secondary to autoimmune/inflammatory syndrome induced by modeling substances (ASIA-MS): A short communication of a clinical case series



Ana Lilia Peralta-Amaro^{a,b,*}, Olga Lidia Vera-Lastra^{a,b}, Nayeli Flores-Flores^{a,b},
Abihai Lucas-Hernández^c, Marcos Osvaldo Molina-Chávez^{a,b}, José Emmanuel Zúñiga Espinosa^{a,b},
Humberto Anduaga-Domínguez^d

^a Division of Postgraduate Studies, Universidad Nacional Autónoma de México, Mexico City, Mexico

^b Internal Medicine Department, Hospital de Especialidades Dr. Antonio Fraga Mouret, Centro Médico Nacional "La Raza", Instituto Mexicano del Seguro Social, Mexico City, Mexico

^c Internal Medicine Department, Hospital General de Teziutlán, Puebla, Mexico

^d Plastic Surgery Department, Hospital de Especialidades Dr. Antonio Fraga Mouret, Centro Médico Nacional "La Raza", Instituto Mexicano del Seguro Social, Mexico City, Mexico

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ABSTRACT

Introduction: Autoimmune/inflammatory syndrome induced by modeling substances (ASIA-MS) is a health problem in many countries. Chronic immune activation caused by these substances has been implicated not only in autoimmune disease development but, in rare cases, also in malignancy.

Materials and methods: A descriptive, retrospective and cross-sectional study was conducted, including 111 patients with ASIA-MS. Demographic, clinical, and immunological variables were collected, and the presence of autoimmune diseases and neoplasms was evaluated.

Results: The 9.9% developed well-defined autoimmune diseases (systemic lupus erythematosus, systemic sclerosis, rheumatoid arthritis, autoimmune hyperthyroidism, and sarcoidosis) and 7.2% developed malignancies (lymphoma, breast cancer, melanoma, chondrosarcoma, intestinal adenocarcinoma, and ovarian cancer).

Conclusion: Although a causal relationship cannot be inferred due to the study design, these findings suggest a possible association between chronic immune stimulation induced by modeling substances and the subsequent development of autoimmunity or malignancy.

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Enfermedades autoinmunes y malignas secundarias al síndrome autoinmune/inflamatorio inducido por modelantes (ASIA-MS): una serie de casos retrospectiva

RESUMEN

Introducción: El síndrome autoinmune/inflamatorio inducido por sustancias de modelado (ASIA-MS) representa un problema de salud en muchos países. La activación inmune crónica causada por estas sustancias se ha implicado no solo en el desarrollo de enfermedades autoinmunes, sino también, en casos poco frecuentes, en la aparición de neoplasias malignas.

Material y métodos: Estudio descriptivo, retrospectivo y transversal que incluyó a 111 pacientes con diagnóstico de ASIA-MS. Se recopilieron datos demográficos, clínicos e inmunológicos, y se analizó la presencia de enfermedades autoinmunes y malignas.

Resultados: El 9,9% desarrolló enfermedades autoinmunes bien definidas (lupus eritematoso sistémico, esclerosis sistémica, artritis reumatoide, hipertiroidismo autoinmune y sarcoidosis) y el 7,2% desarrolló neoplasias malignas (linfoma, cáncer de mama, melanoma, condrosarcoma, adenocarcinoma intestinal y cáncer de ovario).

Palabras clave:

Sustancias de modelado
Cáncer
Inflamación crónica
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Metil metacrilato

* Corresponding author.

E-mail address: ana.peralta22@comunidad.unam.mx (A.L. Peralta-Amaro).

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Conclusión: Aunque no puede inferirse una relación causal debido al diseño del estudio, estos hallazgos sugieren una posible asociación entre la estimulación inmune crónica inducida por sustancias de modelado y el desarrollo posterior de autoinmunidad o malignidad.

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Introduction

Currently, body enhancement and beautification are made possible through surgical techniques developed by plastic and reconstructive surgeons, who perform them safely while safeguarding patients' health, and minimizing risks and complications. However, individuals without medical training often perform unsafe body-modification procedures, such as the infiltration of various substances, which pose health risks and, in some cases, can even lead to death.

Modeling agent-related disease (MARD) is a deforming, disabling, and sometimes fatal condition that results from the infiltration of substances into the body for esthetic purposes. This infiltration leads to local symptoms—such as pain, redness, swelling, and ulcers—as well as systemic manifestations including arthralgia, myalgia, Raynaud's phenomenon, fever, chronic fatigue, sleep disturbances, sicca symptoms, oral ulcers, and myositis. These symptoms result from an immune response triggered by the infiltrated substance, which may even progress to the development of well-defined autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc), Sjögren's syndrome, vasculitis, primary biliary cholangitis (PBC), sarcoidosis, among others.¹ Currently, MARD is recognized within the spectrum of autoimmune/inflammatory syndrome induced by adjuvants (ASIA), as it meets key diagnostic criteria, including specific histopathological findings and clinical improvement following removal of the antigenic agent.^{1,2}

On the other hand, the infiltration of modeling substances has also been associated with the development of certain types of malignancies in both animal models and humans. For example, mineral oil (MO) infiltration has been linked to the development of plasmacytoma, multiple myeloma, and squamous cell carcinoma,^{3–6} whereas methyl methacrylate infiltration has been associated with B-cell lymphoma.⁷ This is likely due to chronic immune stimulation caused by the developed autoimmune disease and the modeling substances themselves, leading to a persistent inflammatory state—recognized as one of the hallmarks of cancer development.^{8,9} In addition, modeling substances, as xenobiotic factors, may induce chronic cellular damage through various mechanisms, including inflammation, oxidative stress, direct genotoxicity, or the secretion of oncogenic products, all of which contribute to tumorigenesis.⁸

Therefore, we aimed to analyze a retrospective group of patients with autoimmune/inflammatory syndrome induced by modeling substances (ASIA-MS) to determine the frequency of both autoimmune and malignant diseases within this population.

Materials and methods

A retrospective cross-sectional study was conducted at a tertiary hospital, including patients diagnosed with ASIA-MS injected for cosmetic purposes, and treated between January 2012 and June 2023 by the Plastic and Reconstructive Surgery and Internal Medicine departments at the Hospital de Especialidades del Centro Médico Nacional 'La Raza'. All patients fulfilled Shoenfeld's diagnostic criteria for ASIA,¹ which include both local and systemic manifestations secondary to exposure to modeling substances. The initial ASIA-MS presentation in all cases

involved local inflammatory reactions at the injection sites, with or without systemic symptoms such as arthralgia, myalgia, chronic fatigue, or sicca symptoms.¹ The diagnosis of autoimmune diseases was established according to internationally accepted criteria: systemic lupus erythematosus (EULAR/ACR 2019), systemic sclerosis (ACR/EULAR 2013), rheumatoid arthritis (ACR/EULAR 2010), autoimmune hyperthyroidism (ATA 2016), and sarcoidosis (ATS/ERS/WASOG 2020 clinical practice guideline). Patients aged 18 years or older of either sex were included. Patients with a prior diagnosis of autoimmune or oncologic disease, those who discontinued medical follow-up in the treatment departments, and those with breast implants were not included.

The study variables obtained from electronic medical records included age, sex, family history of autoimmune or oncologic diseases, type and volume of modeling substance injected, affected anatomical area, local and systemic symptoms, the time interval between injection and symptom onset, and the type of medical and surgical treatment received. We identified the specific autoimmune and oncologic diseases that developed during the follow-up period.

Statistical analysis

Descriptive statistical analysis was performed via SPSS version 25. Categorical variables are expressed as absolute numbers and percentages. The distribution of quantitative variables was assessed via the Kolmogorov–Smirnov test. Depending on the distribution, quantitative variables are reported as the mean and standard deviation (for normally distributed data) or as the median and interquartile range (for nonnormally distributed data).

Results

We included 111 patients with ASIA-MS; 100 (90.1%) were women, and 11 (9.9%) were men, with a mean age of 54 ± 12 years. Eight (7.2%) patients had a first-degree family history of cancer, and another eight (7.2%) patients had cancer (Table 1).

The median time between the injection of the modeling agent and the onset of symptoms was 10 (1–38) years. The majority of patients (92.8%) received injections with only one type of modeling agent, while the remaining 7.2% received two types. MO was the most frequently injected modeling agent (62.2%), followed by silicone (16.2%). Less commonly used agents were reported in smaller proportions. Six patients (5.4%) were unaware of the specific agent injected. Regarding the volume administered, 82% of patients received more than 300 ml, 14.5% received 100–300 ml, and 3.6% received less than 100 ml. In terms of anatomical distribution, 73% of patients had injections at a single site. The buttocks (65.8%) and breasts (46.8%) were the most commonly affected areas.

The most frequently reported local manifestations were local pain (98.2%), tumor formation (94.6%), and skin discoloration (77.5%). All patients underwent some form of surgical treatment, with granuloma resection being the most common procedure (73.9%). Furthermore, 74.8% of patients required reconstructive surgery, including local flap reconstruction (45%) and final reconstruction with silicone breast implants (30.6%). Only 25 patients

Table 1
Demographic, clinical, and therapeutic features in patients with ASIA-MS.^a

n = 111 (100%)	
<p>Demographic characteristics</p> <ul style="list-style-type: none"> • Age, years: 54 ± 12 • Female: 100 (90.1%) • Male: 11 (9.9%) • Family history of cancer^b: 8 (7.2%) • Diagnosis time, years^c: 10 (1–38) <p>Number of modeling agents</p> <ul style="list-style-type: none"> • One type: 103 (92.8%) • Two types: 8 (7.2%) <p>Type of modeling agent</p> <ul style="list-style-type: none"> • Not identified: 6 (5.4%) • Mineral oil: 69 (62.2%) • Silicon: 18 (16.2%) • Vegetable oil: 6 (5.4%) • Bovine fat: 5 (4.5%) • Collagen: 5 (4.5%) • Methacrylate: 4 (3.6%) • Carnitine: 2 (1.8%) • Guaiacol: 2 (1.8%) • Hyaluronic acid: 1 (0.9%) • Artichoke: 1 (0.9%) • Iodine: 1 (0.9%) <p>Volume of modeling agent</p> <ul style="list-style-type: none"> • >300 ml: 91 (82%) • 100–300 ml: 16 (14.4%) • <100 ml: 4 (3.6%) <p>Number of infiltrated sites</p> <ul style="list-style-type: none"> • One: 81 (73%) • Two: 28 (25.2%) • Three: 2 (1.8%) <p>Site of infiltration</p> <ul style="list-style-type: none"> • Buttocks: 73 (65.8%) • Breast: 52 (46.8%) • Calves: 10 (9%) • Thighs: 3 (2.7%) • Face: 3 (2.7%) • Thorax: 1 (0.9%) 	<p>Clinical manifestations</p> <ul style="list-style-type: none"> • Local manifestations <ul style="list-style-type: none"> ○ Local pain: 109 (98.2%) ○ Tumor formation: 105 (94.6%) ○ Skin color change: 86 (77.5%) ○ Deformity: 55 (49.5%) ○ Local infection: 49 (44.1%) ○ Hyperemia: 38 (34.2%) ○ Migration of the modeling agent: 8 (7.2%) • Systemic complications <ul style="list-style-type: none"> ○ Cancer: 8 (7.2%) ○ Autoimmune disease: 11 (9.9%) <p>Immunosuppressive therapy</p> <ul style="list-style-type: none"> • None: 86 (77.5%) • Methotrexate: 15 (13.5%) • Azathioprine: 6 (5.4%) • Chloroquine: 4 (3.6%) • Mycophenolate mofetil: 2 (1.8%) • Cyclosporine: 1 (0.9%) • Colchicine: 1 (0.9%) • Sulfadiazine: 1 (0.9%) • Etanercept: 1 (0.9%) • Leflunomide: 1 (0.9%) <p>Surgical therapy</p> <ul style="list-style-type: none"> • Resection of granulomas: 82 (73.9%) • En bloc resection: 29 (26.1%) • Mastectomy: 44 (39.6%) <p>Reconstructive surgery</p> <ul style="list-style-type: none"> • None: 28 (25.2%) • Reconstruction with local flap: 50 (45%) • Final reconstruction with SBI^d: 34 (30.6%) • Autologous fat graft: 22 (19.8%) • Skin graft: 11 (9.9%)

^a ASIA-MS: autoimmune/inflammatory syndrome induced by modeling substances.

^b First-degree family.

^c Time elapsed between the infiltration of the modeling agent and the diagnosis of ASIA-MS.

^d SBI: silicone breast implants.

(22.5%) received immunosuppressive therapy. Further details are presented in Table 1.

Table 2 shows the autoimmune and oncological diseases identified in the patients, along with the type and quantity of modeling agent injected, the anatomical site, and the time elapsed since injection. MO was the most frequently identified modeling agent (9 out of 17). Except for two patients, all patients received injections of more than 300 ml of modeling agent. The buttocks were the most commonly injected site (11 out of 17), followed by the breasts (8 out of 17).

Discussion

This case series describes a cohort of patients diagnosed with ASIA-MS, focusing on the clinical spectrum and highlighting the occurrence of both autoimmune and malignant diseases in this population. Modeling substances have been recognized as adjuvants capable of inducing chronic inflammation and autoimmunity, processes that may, in certain cases, contribute to oncogenesis. In recent years, an increasing variety of injected modeling agents have been reported, including MO, vegetable oil, bovine fat, guaiacol, paraffin, liquid silicone, hyaluronic acid, polyacrylamide hydrogels, poly-L-lactic acid, polyalkylimide, collagen, hydroxyapatite, and methyl methacrylate.^{1,7,10}

Currently, ASIA-MS is considered a public health problem because of the absence of effective health policies regulating the use and administration of modeling substances, which has led to an increase in the number of reported cases worldwide.² ASIA-MS is a deforming and disabling disease, with both local and systemic manifestations that significantly impact patients' well-being. In addition to the development of autoimmune diseases, these individuals also may face an increased risk of developing malignant neoplasms.

Some well-defined autoimmune diseases confer a greater risk for cancer development, such as autoimmune hepatitis and PBC for hepatocellular carcinoma, autoimmune gastritis for gastric cancer, and Crohn's disease and ulcerative colitis for colon cancer. Additionally, dermatomyositis, RA, SSc, SLE, and type 1 diabetes increase the risk of various types of cancer.⁸ In general, autoimmune diseases increase the risk of developing cancer by 3.3–12-fold compared with the general population.^{8,11} In our cohort, ASIA-MS typically began with local inflammatory reactions and nonspecific systemic manifestations, followed, in some cases, by the development of well-defined autoimmune diseases. This supports the concept of ASIA-MS as a clinical spectrum in which chronic immune stimulation induced by foreign substances may evolve toward systemic autoimmunity in genetically or immunologically susceptible individuals.^{1,2,7}

Table 2
Systemic autoimmune and neoplastic diseases in patients with ASIA-MS.^a

Type	Modeling agent	Quantity (milliliters)	Place of infiltration	Years to diagnosis of ASIA-MS	Family history of cancer	
<i>Oncological disease</i>						
1	Chondrosarcoma	Mineral oil	>300	Buttocks	26	Lung and stomach
2	Intestinal adenocarcinoma	Mineral oil	>300	Buttocks	17	None
3	Melanoma	Mineral oil	>300	Breast and buttocks	6	Skin
4	Breast cancer	Mineral oil	100–300	Breast	1	Liver
5	Breast cancer	Silicon	>300	Breast	3	None
6	DLBCL ^b	Methacrylate	>300	Buttocks	6	None
<i>Autoimmune and oncological disease</i>						
7	SSc ^c and ovarian cancer	Mineral oil	>300	Buttocks and calves	7	Colon
8	SSc ^c and angioimmunoblastic lymphoma	Bovine fat	>300	Breast and buttocks	7	None
<i>Autoimmune disease</i>						
9	SLE ^d	Silicon	>300	Buttocks	4	None
10	SLE ^d and interstitial lung disease	Mineral oil	>300	Buttocks	20	Cervical and skin cancer
11	SLE ^d	Mineral oil	>300	Breast	20	None
12	Rheumatoid arthritis	Mineral oil	>300	Breast	12	None
13	Rheumatoid arthritis	Silicon	>300	Buttocks	6	None
14	Systemic sclerosis	Silicon	>300	Buttocks	11	None
15	Hyperthyroidism	Mineral oil and silicon	>300	Breast	8	Non-Hodgkin lymphoma
16	Hyperthyroidism	Bovine fat	>300	Buttocks	25	None
17	Sarcoidosis	Carnitine	<100	Breast and face	4	None

^a ASIA-MS: autoimmune/inflammatory syndrome induced by modeling substances.

^b Diffuse large B-cell lymphoma.

^c Systemic sclerosis.

^d Systemic lupus erythematosus.

In this descriptive study, 9.9% of patients developed a well-defined autoimmune disease, including SLE, SSc, RA, hyperthyroidism, and sarcoidosis. The frequency of cancer was 7.5%, with identified cases including lymphoma, breast cancer, melanoma, chondrosarcoma, intestinal adenocarcinoma, and ovarian cancer. The modeling substances associated with these diseases are MO, silicone, methyl methacrylate, bovine fat, and carnitine.

Chronic and sustained inflammation caused by autoimmune diseases, as well as persistent cellular damage induced by modeling substances through oxidative stress, direct genotoxicity, and the secretion of oncogenic factors, can lead to tumorigenesis.^{8,9} The link between inflammation and cancer is well-documented through several mechanisms: (1) The continuous production of reactive oxygen and nitrogen species, which cause DNA damage, mutations, and genomic instability. (2) The release of cytokines and growth factors by inflammatory cells, such as macrophages and neutrophils, promotes cell proliferation, inhibits apoptosis, and promotes angiogenesis, all of which contribute to tumor progression. (3) Chronic inflammation creates an immunosuppressive microenvironment that prevents the immune system from effectively attacking and destroying cancer cells. (4) Remodeling of extracellular matrix components and altering matrix metalloproteinases facilitate cancer spread.^{8,9,12–14}

Moreover, autoimmunity-induced tumorigenesis begins with cellular injury mediated by autoantigen-specific T cells or antibodies driven by any of the three types of immunological profiles: type 1, 2 and 3 immunity. Type 2 immunity involves CD4+ helper T cells (Th2), group 2 innate lymphoid cells (ILC2s), follicular helper T cells, basophils, or mast cells that produce the critical type 2 cytokines interleukin (IL)-4 and IL-13. In acute situations, type 2 immunity is beneficial for combating infections and promoting wound healing. However, in chronic settings, the effects of type 2 immunity are not so “benign” and can lead to abnormal cell lineage differentiation and tumorigenesis; this has been supported by experimental evidence from mouse models with CTLA4 deficiency.⁸

In the context of ASIA-MS, the mechanisms of tumorigenesis may differ between lymphoproliferative and solid malignancies. Lymphoproliferative disorders, such as lymphoma and multiple myeloma, are thought to arise from chronic antigenic stimulation and sustained B-cell activation leading to clonal expansion and genomic instability within germinal centers. Continuous immune activation and prolonged inflammatory signaling may promote the survival of autoreactive B-cell clones that can undergo malignant transformation.^{4,11}

Solid tumors (e.g., breast, intestinal, and ovarian cancers, melanoma, and chondrosarcoma) are more closely associated with

chronic tissue injury, oxidative stress, and cytokine-mediated cellular proliferation. The persistent generation of reactive oxygen and nitrogen species causes DNA damage and epigenetic alterations, while proinflammatory mediators such as TNF- α , IL-1 β , and IL-17 enhance angiogenesis, inhibit apoptosis, and remodel the extracellular matrix processes that collectively promote tumor progression and metastasis.^{8,9,12–14}

These mechanisms, together, support the concept that chronic inflammation induced by foreign modeling substances may establish a protumorigenic microenvironment that favors both lymphoid and non-lymphoid malignancies in genetically or immunologically predisposed individuals.

Among the population studied, we identified patients with various types of cancer, for which possible mechanisms of development have been described. MO was the most frequently implicated modeling substance. Importantly, MO has been recognized as a genotoxic carcinogen.¹⁵ Additionally, we observed that, except for one patient, all the patients had received more than 300 ml of modeling agent. Other factors that may have contributed to the development of autoimmunity and malignancy in these patients include genetic predisposition, family history of autoimmune or oncologic diseases, smoking, chronic infections, and hormonal therapies. These variables were not systematically assessed in this cohort, representing an area for future research.

Conclusions

This descriptive case series underscores the serious health risks of modeling substances used for esthetic purposes, including deformity, disability, autoimmune and oncological diseases, treatment-related complications, reduced quality of life, and increased mortality. It highlights the urgent need for greater awareness and stricter regulatory policies to address the dangers of unregulated body modification practices.

Limitations

The limitations of our study are primarily related to its retrospective and purely descriptive design, based on a review of medical records. Recall bias is present, as some patients were unaware of the type of modeling substance used, and the reported volumes may be inaccurate. Due to the retrospective nature of the study, viral serologies such as Epstein-Barr virus (EBV), hepatitis C virus (HCV), and other oncogenic viruses were not available for most patients. This limits the evaluation of potential viral contributions to the development of autoimmunity or malignancy and should be addressed in future prospective studies. The small sample size and study design do not allow for the establishment of causal relationships between variables, but this study represents an initial step toward raising awareness about the potential development of malignancies in patients with ASIA-MS.

Authors' contributions

All the authors contributed to the drafting or revision of the article, and all the authors approved the final version to be published.

Ana Lilia Peralta-Amaro: study conceptualization; visualization; data collection; statistical analysis; review; and editing of the original draft.

Nayeli Flores-Flores: study conceptualization; visualization; data collection; statistical analysis; review; and editing of the original draft.

Abihai Lucas-Hernández: reviewed and edited the original draft.

Marcos Osvaldo Molina-Chávez: reviewed and edited the original draft.

José Emmanuel Zúñiga Espinosa: visualization, data collection.

Humberto Anduaga-Domínguez: conceptualization and editing of the original draft.

Olga Lidia Vera-Lastra: conceptualization; supervision; writing and editing of the original draft.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and approved by our institution's Ethics Committee (Comité Local de Investigación en Salud 3501 Instituto Mexicano del Seguro Social) Registered number R-2022-3501-170.

Informed consent statement

Informed consent was obtained from all the subjects.

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Data availability

All presented data are original and accessible upon reasonable request.

Conflict of interest

None.

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