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ORIGINAL ARTICLE
Research

Classification for Staging and Managing Patients with Biopolymer-induced Human Adjuvant Disease

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Background: Biopolymer-induced human adjuvant disease (BHAD) is a chronic clinical condition that requires surgical intervention, regardless of the presence of symptoms, to minimize the risk of functional, aesthetic, and systemic sequelae and the development of conditions simulating autoimmune disease. We propose a classification for BHAD on the basis of course of the disease, which will make it possible to assess the damage and difficulty in patients, leading to a more appropriate therapeutic approach.

Methods: A protocol study was implemented. A casuistry of patients with a diagnosis of autoimmune/inflammatory syndrome induced by adjuvants was taken into account according to the Shoenfeld criteria. Qualitative variables were analyzed through frequencies and percentages, and quantitative variables were analyzed with measures of central tendency and dispersion. The diagnostic validity of the signs and symptoms was analyzed using some paraclinical tests.

Results: A total of 190 patients diagnosed with autoimmune/inflammatory syndrome induced by adjuvants with biopolymers in the buttocks and who underwent a surgical procedure by the open, masked technique between January 2017 and December 2020 were selected. Considering each sign and symptom, the location of the biopolymers in different planes, and pathophysiology of the clinical course of the disease, a classification was proposed that takes into account diagnostic imaging findings, local clinical signs, systemic symptoms, systemic clinical signs, and autoimmune markers.

Conclusion: Some signs associated with biomarkers with sensitivity and specificity values can influence the pretest decision to request paraclinicals, improving the diagnostic probability and cost effectiveness in these patients. *(Plast Reconstr Surg Glob Open 2022;10:e4137; doi: 10.1097/GOX.0000000000004137; Published online 24 February 2022.)*

INTRODUCTION

Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) is a broad and general classification that is used to categorize four major syndromes caused due to an immune response to adjuvants—autoimmune macrophagic myofasciitis, silicosis, post-vaccination syndrome, and Gulf War illness.[1] Although this classification has been extrapolated and used for patients with biopolymers, it does not cover specific aspects of biopolymer-induced human adjuvant disease (BHAD).[2]

BHAD is a chronic clinical condition that requires surgical intervention as treatment in 100% of the affected population, regardless of whether they are symptomatic or asymptomatic, to minimize the risk of local and systemic sequelae and the risk of developing conditions that simulate the clinical course of disease of autoimmune etiology.[3] Through the study of the clinical and immunological nature of the disease, ASIA has certain criteria for its diagnosis,[4–7] but this does not enable staging of the degree of severity that guides the treatment required for the patient. Consequently, it is necessary to create a classification for BHAD on the basis of the nature of the disease that will make it possible to assess the damage and difficulty in the patients, leading to a more appropriate therapeutic approach. The objective of this study is to establish a scale to assess the severity of BHAD based on the natural history of the disease.

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Received for publication September 21, 2021; accepted December 14, 2021.

DOI: 10.1097/GOX.0000000000004137

Disclosure: *The authors do not have financial interest to declare in relation to the content of this article.*

This study was carried out from the observational clinical follow-up of patients with BHAD since 2017. Different stages of the disease were noted that helped in surgical practice, enabling an understanding of the sequence of appearance of signs and symptoms,[6,7] positivity of immunological markers, and the natural course of the disease, taking into account the findings and consistency with the pathophysiology with which a disease staging scale shall be proposed (Tables 1–3). This is due to the fact that a gold standard has not yet been established that makes it possible to compare findings; however, the purpose of the present study was to explore the research field in relation to BHAD.[3]

METHODS

The study took into account a casuistry of patients diagnosed with ASIA according to the Shoenfeld criteria who underwent a surgical procedure for biopolymer removal in a plastic surgery clinic in Bogotá, Colombia from 2017 to 2020. These data were used to establish a case definition of BHAD, which was also based on the pathophysiology of the disease. The patients included had complete clinical history data, including data on presurgical assessment of plastic surgery and aesthesia and laboratory parameters. Patients with uncontrolled diabetes, arterial hypertension, thyroid disease, active infection located at the site of administration of the biopolymer, hemoglobin levels less than 12.5 mg per dL, or diagnosis of human immunodeficiency virus were excluded. We excluded these cases so as not to generate confounding biases that could alter the relationships that are the object of this work. In addition, initially, we did not operate on this type of patient if they did not have their comorbidities under control—for example, glycosylated hemoglobin less than 5.8%, thyroid stimulating hormone in normal parameters, undetectable viral load, and CD4 counts greater than 800—minimize complications (Table 4).

The surgical technique used in these patients for biopolymer removal was the Meticulous Approach Safer and Keeper (MASK) technique, which has six main objectives: to remove as much biopolymer compromised tissue as possible, to minimize esthetic sequelae, to improve the local compartment syndrome produced in the area of administration, to improve local and systemic symptoms with consequent recovery of functionality and positively impact the patient's quality of life, to manage the migration pattern of the product, and finally, to provide the best possible esthetic result.[3] The structure of the scale is based on local and systemic signs and symptoms, radiology imaging and paraclinical studies, each of which is assigned a score that will be used to determine the degree of severity. Qualitative variables were analyzed through frequencies and percentages, and quantitative variables were analyzed with measures of central tendency and dispersion. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of each of the signs and symptoms were calculated for being

Takeaways

Question: To propose a classification for biopolymer-induced human adjuvant disease (BHAD).

Findings: A transversal study in a total of 190 patients diagnosed with ASIA with biopolymers in the buttocks and who underwent a surgical procedure by the open, masked technique between January 2017 and December 2020 was conducted, taking into account diagnostic imaging findings, local clinical signs, systemic symptoms, systemic clinical signs, and autoimmune markers. Some signs associated with biomarkers with sensitivity and specificity values can influence the pretest decision to request paraclinicals, improving the diagnostic probability and cost effectiveness in these patients.

Meaning: The Pachón classification can be a useful tool for the diagnosis and treatment of BHAD.

Table 1. Frequency of Local Signs in Biopolymer-induced Human Adjuvant Disease (BHAD)

Local Clinical Signs	Quantity	Percentage
Satellite adenopathies	190	100.0
Erythema	178	93.7
Telangiectasias	177	93.2
Cutaneous venous dilatations	165	86.8
Eczema	162	85.3
Pachydermostosis	155	81.6
Morpheas	108	56.8
Necrosis	5	2.6
Epidermolysis	4	2.1

Table 2. Frequency of Symptoms in Biopolymer-induced Human Adjuvant Disease (BHAD)

Systhemic Symptoms	Quantity	Percentage
Mialgias	175	92.1
Arthralgias	148	77.9
Asthenia	148	77.9
Adinamia	148	77.9
Headache	71	37.4
Abdominal distension	76	40.0
Hair loss	48	25.3
Fever	21	11.1
Photophobia	54	28.4
hyperacusis	51	26.8
Dry mouth	21	11.1
Memory loss	15	7.9
Neuropathic pain	105	55.3
Sympathetic-reflex dystrophy	1	0.5
Causalgia	1	0.5

Table 3. Frequency of Systemic Clinical Signs in Biopolymer-induced Human Adjuvant Disease (BHAD)

Systemic Clinical Signs	Quantity	Percentage
Urticariform lesions	16	8.4
Petechiae	5	2.6
Vascular nodules	27	14.2
Porcelain scleras	23	12.1
Raynaud's phenomenon without rheumatologic history	22	11.6
Jaundice	9	4.7
Skin rashes	5	2.6
Terry's nails	2	1.1

Table 4. Frequency of Autoimmune Markers in Biopolymer-induced Human Adjuvant Disease (BHAD)

Autoimmune Markers	Quantity	Percentage
Negative	76	40
Antinuclear antibodies	114	60.0
Lupus anticoagulant	27	14.2
Serum complement C3-C4	8	4.2
anti SLC-70 antibodies	5	2.6
Rheumatoid factor	4	2.1
lactate dehydrogenase	38	20.0
HLA – B27 (+)	5	2.6
Antithyroid peroxidase antibodies	3	1.6
Glycosylated hemoglobin	3	1.6
Carcinoembryonic antigen	2	1.1
Alkaline phosphatase beta fraction	1	0.5

positive for antinuclear antibodies, lactate dehydrogenase, and lupus anticoagulant. The results are presented in tables and graphs, supported by images of the different skin stages[8–11] (Figs. 1–5). Some systemic manifestations are also supported in Figures 6 and 7.

A case definition was created based on patients with a history of bearing biopolymers between 6 and 14 years. Patients presenting one or more of the following symptoms: myalgia, arthralgia, asthenia, adynamia, and predominantly sensitive neurological symptoms; positive for any of the following: ANAs, complement proteins C3 and C4, LDH, lupus anticoagulant, or rheumatoid factor; and showing improvement with removal of the material were selected for the study.[3]

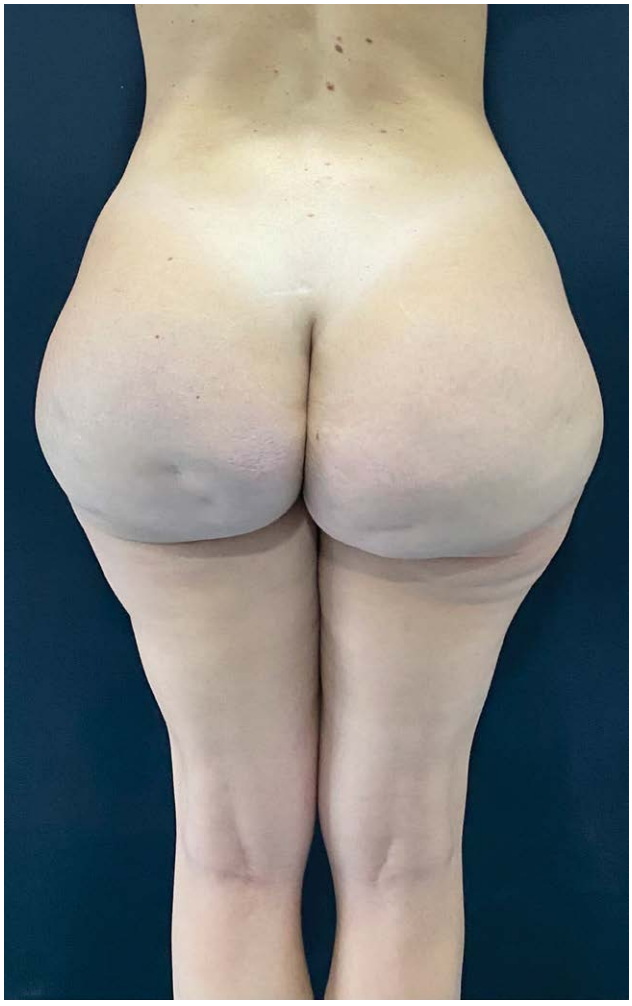

Fig. 1. No signs of skin damage.

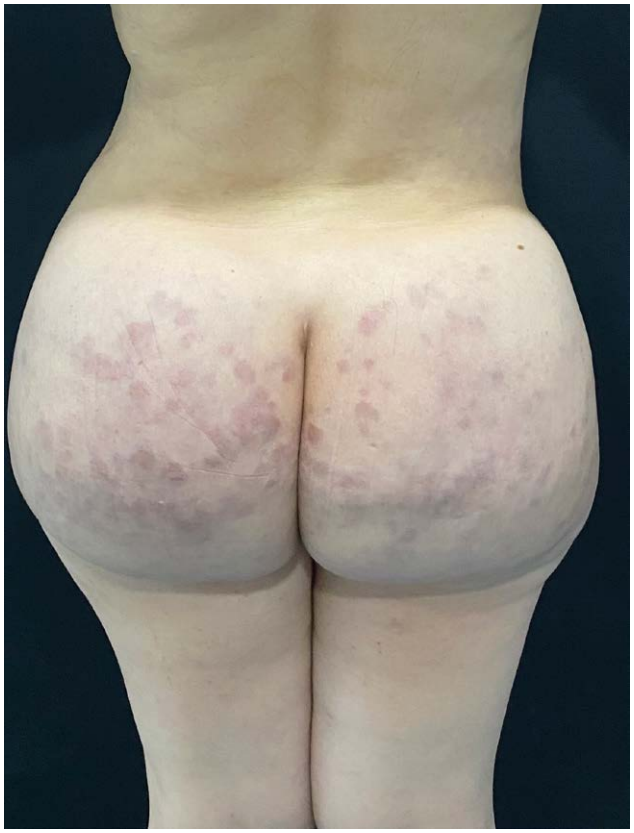

Fig. 2. Eczema.

RESULTS

The study sample was composed of 190 patients diagnosed with ASIA with biopolymers in the buttocks and who underwent a surgical procedure by Dr. Jaime Pachón's open MASK technique between January 2017 and December 2020. In total, 98.4% of patients were women, with a mean age of 41 ± 10.3 (SD) years, and were of various nationalities with the majority being Colombian (120 patients) (63, 16%).

Taking into account the frequencies of the appearance of each of the signs and symptoms, location of the biopolymers in different planes, and pathophysiology of the clinical behavior of the disease, the Pachón classification proposes taking five parameters into consideration: (1) diagnostic imaging findings (MRI), (2) local clinical signs, (3) systemic symptoms, (4) systemic clinical signs, and (5) autoimmune markers (Table 5).[8–15] This assessment makes it possible to generate a score that categorizes the biopolymer carrier patient with a stage of the disease (mild, moderate, or severe), which in turn allows us to establish an individualized treatment plan (Tables 6, 7).

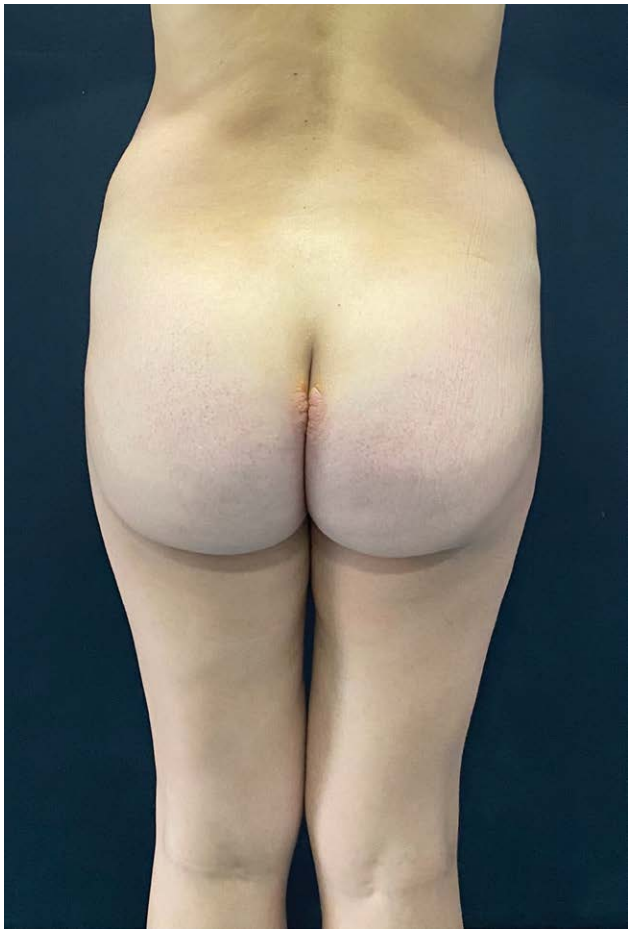

Fig. 3. Pachyderm skin.

Table 8 shows that the sensitivities and specificities of the signs and symptoms are low; however, the PPVs and NPVs of certain signs and symptoms can help in making decisions when thinking about the need to request a diagnostic test. We have reported cases with a history of dry eye, porcelain sclera, memory loss, and necrosis, which had NPV greater than 80%. Moreover, eczema, erythema at the site of the biopolymer, and telangiectasia had PPVs that were also considered good (Table 8).

When the signs and symptoms were evaluated in the sensitivity analysis for the estimation of LDH positivity,[9,11] it was shown that adynamia, neurological symptoms, pachydermostosis, nodules, and headache can show sensitivities greater than 80%. Petechiae was the only clinical sign with 100% sensitivity.[15,16] In the same way, PPVs were good in patients with eczema and pachydermostosis; finally, memory loss, dry mouth, presence of nodules, and necrosis were favorable, ruling out the disease in their absence due to NPV greater than 80% (Table 9).

In contrast, for lupus anticoagulant, the signs and symptoms showed high values in specificity; however, the signs with higher PPVs were telangiectasias and myalgias, and those with higher NPVs were dry eye, porcelain sclera, necrosis, and dry mouth (Table 10).

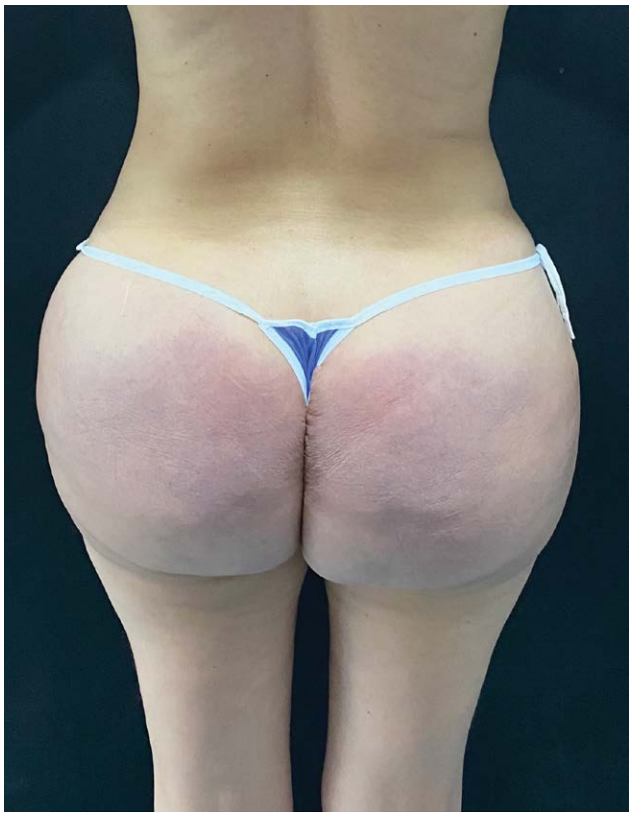

Fig. 4. Morpheas.

DISCUSSION

BHAD needs to be considered a public health problem that affects the quality of life and functionality of patients, causing an impact not only on the individual, but also on their family, work environment, and economic productivity. This creates the need to establish worldwide governmental strategies that include prohibition of the administration of biopolymer in the human body through the regulatory entities for substances and drugs in each country, taking into account the alerts issued by the Food and Drug Administration in which emphasis is placed on the danger these products pose.[17] Surgical management for the removal of these materials should be safely implemented in both symptomatic and asymptomatic patients, so as to reduce morbidity as well as functional and aesthetic sequelae.[18–20]

The previous classifications proposed by Shoenfeld and Alijotas[18–20] raised the possibility of associating symptoms and paraclinical studies with rheumatological conditions. However, there is a need to create a specific and directed classification of these nonbiocompatible products in the population with biopolymers, which trigger signs and symptoms in the affected population with positive paraclinical studies for immunological conditions.

This study proposes a classification that takes into account severity levels based on the natural course of the disease, evaluated in a cohort of patients from a plastic surgery clinic in Colombia from 2017 to 2020 to stage the damage caused by these materials and the

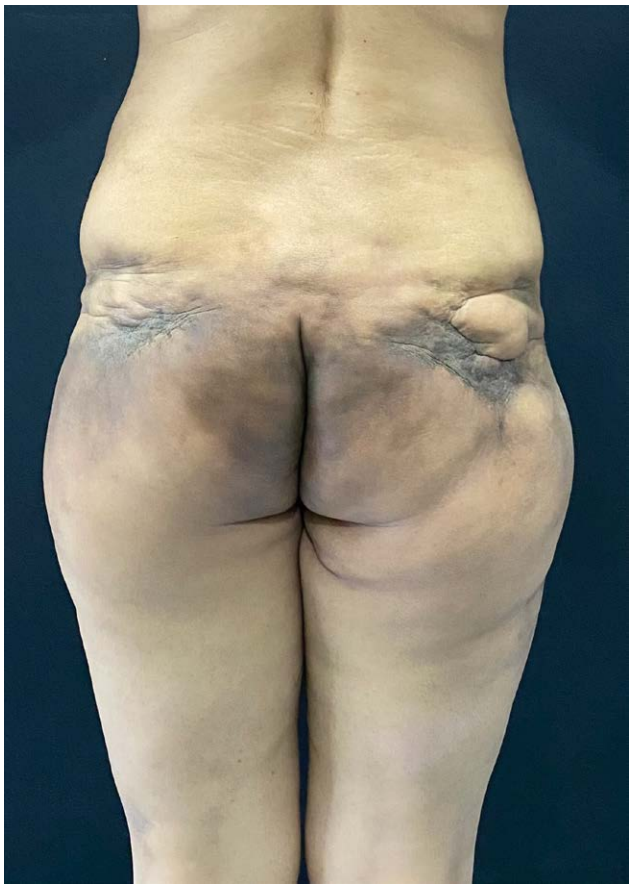

Fig. 5. Necrosis.

corresponding treatment. Consequently, three color-coded levels were created; there was no green level because it was assumed that the patient has a material that is not biocompatible with the body. There is a cellular or humoral autoimmune response established from the moment of administration of biopolymer that may be asymptomatic, and it was assumed that all cases of BHAD were mild to severe.

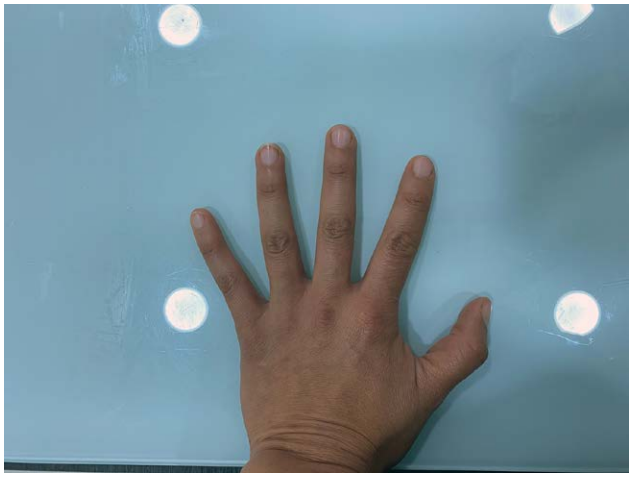

Fig. 6. Terry's nails.

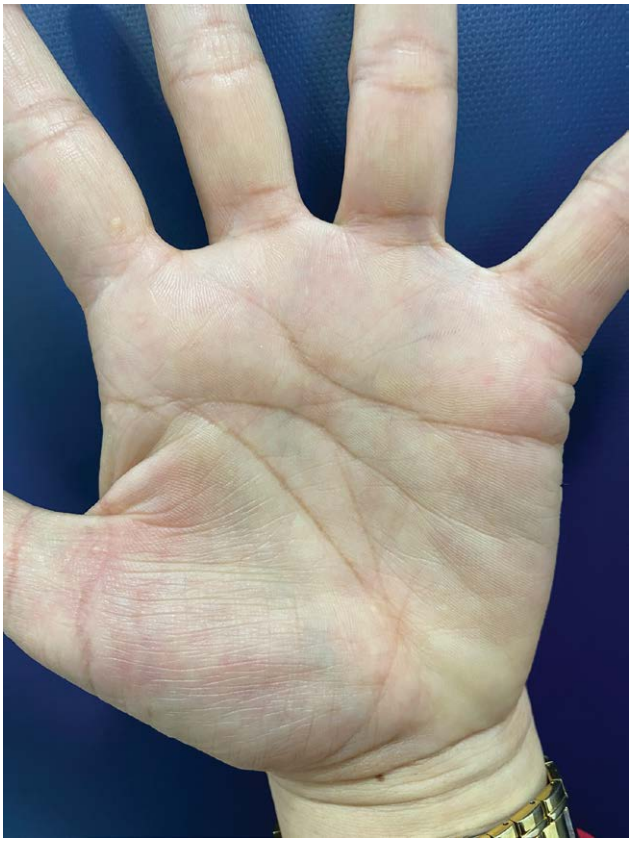

Fig. 7. Hand eczema.

The mild stage of the Pachón classification suggests surgical management without clinical rheumatological intervention; however, a patient who presents some positive immunological paraclinical results and continues to have them post-surgery will require evaluation and follow-up by a rheumatologist. The moderate stage will not only require surgical management with the open technique but also pre- and postoperative rheumatological management with immunomodulatory therapies to mitigate symptoms associated with positive immunological markers. The severe stage will be limited to the management of complications, removal of biopolymer wherever possible, and reconstruction with local or microsurgical flaps as required.

There is no evidence in the literature that patients with ASIA should undergo a multidisciplinary approach for their recovery; however, this study aims at proposing the need for patients with BHAD to have an assessment and follow-up with pain medicine and palliative care, rheumatology, physical rehabilitation therapy, and psychiatry, as

Table 5. Nuclear Magnetic Resonance Localization of Biopolymer

Nuclear Magnetic Resonance	Quantity	Percentage
Biopolymers with local or systemic migration	146	76.8
Biopolymers with muscle fascia infiltration	32	16.8
Biopolymers located in the gluteal region	13	6.8

Table 6. Scoring and Staging of Severity

Clinical and Paraclinical Diagnostic Criteria	Mild (1 Point)	Moderate (2 Point)	Severe (3 Point)
Simple nuclear magnetic resonance with short tau inversion recovery technique or computed tomography with 3D reconstruction that shows the material	Located in the gluteal region	Material with muscle fascia infiltration	Local or systemic migration
Local clinical signs	Satellite lymphadenopathy, erythema, telangiectasia	Varicose cutaneous dilation Biopolymer eczema, pachydermostosis	Morphea, epidermolysis, necrosis
Systemic symptoms	Myalgias Arthralgias Asthenia Adinamia Fever Headache Abdominal distention	Memory loss photophobia Dry mouth Hyperacusis	Loss of visual acuity, neuropathic pain, reflex sympathetic dystrophy, causalgia
Systemic clinical signs	Urticarial lesion, petechiae, hair loss	Vascular nodules, porcelain sclera	Raynaud's phenomenon with no known rheumatologic history, skin rashes, jaundice, Terry's nails
Autoimmune markers	Negative	Antinuclear antibodies Lupus anticoagulant Hypercomplementemia c3-c4, Rheumatoid factor, SLC-70 antibodies for scleroderma	Lactate dehydrogenase HLA - B27 (+) Antiperoxidase antibodies Glycosylated hemoglobin Carcinoembryonic antigen Alkaline phosphatase beta fraction

management not only consists of removing the material, but also rehabilitation and accompaniment to overcome the functional and mental sequelae, thereby establishing the need to create health groups or institutions that are experts in biopolymer removal with a multidisciplinary approach. In addition, all patients should have rheumatology follow-up to monitor autoimmune markers such as ANAs, complement C3 and C4 proteins, and lupus anticoagulant.[3]

According to Pachón et al, BHAD mimics autoimmune diseases with a prevalence of 5.3%, as documented in a plastic surgery clinic in Colombia.[3] This study shows the importance of taking complete clinical history, since it is documented that there are some local and systemic signs and symptoms that can be evaluated for the diagnosis of BHAD, which will help in guiding the pretest need to request some paraclinicals with an autoimmune profile such as antinuclear antibodies, LDH, and lupus anticoagulant.

Table 7. Staging of Severity

Disease Stage	Score	Treatment
Mild	≤4 points	Biopolymer removal with open surgical technique + evaluation by psychiatry and physical rehabilitation
Moderate	5–14 points	Biopolymer removal with open surgical technique + evaluation by rheumatology, psychiatry, and physical rehabilitation therapy
Severe	≥15 points	Biopolymer removal with open surgical technique + reconstruction + reconstruction using local flaps or microsurgery + assessment with pain medicine and palliative care, evaluation by physical rehabilitation therapy, rheumatology, and psychiatry

The decision to request paraclinicals for postoperative follow-up to define whether it is a true autoimmune disease or a simulation will depend on the experience of the physician and the evidence collected. Moreover, this decision will impact the treatment and cost effectiveness.

The general ASIA classifications available for the diagnosis of the disease do not integrate diagnostic images. This study includes MRI findings because they are a presurgical diagnostic aid to evaluate not only the type of material that is expected to be found at the time of surgery, since most patients do not know what it is, but also makes it possible to evaluate the damage at the muscular level and the infiltration of organs or systems, which is directly related to the severity. From this visual assessment, the surgeon can make a plan that enables the maximum removal of the product.

Table 8. Sensitivity Analysis of Signs and Symptoms versus Antinuclear Antibody

	Antinuclear Antibodies			
Clinical Features	Sensitivity	Specificity	PPV	NPV
Adynamia	57.43%	30.95%	74.56%	17.11%
Asthenia	57.43%	30.95%	74.56%	17.11%
Arthralgias	57.43%	30.95%	74.56%	17.11%
Dry eye	55%	39.41%	10%	88.16%
Eczema	59.26%	35.71%	84.21%	13.16%
Erythema	61.24%	58.33%	95.61%	9%
Porcelain sclerae	65.22%	40.72%	13.16%	89.47%
Fever	52.38%	39.05%	10%	86.84%
Hair loss	64.58%	41.55%	27.19%	77.63%
Memory loss	60%	40%	8%	92.11%
Morphea	58.72%	38.27%	56.14%	40.79%
Necrosis	40%	39.46%	2%	96.05%
Neurological symptoms	55.24%	34.52%	51.33%	38.16%
Pachydermostosis	58.06%	31.43%	78.95%	14.47%
Abdominal distension	52%	34.78%	34.21%	52.63%
Photophobia	53.70%	37.78%	25.66%	67.11%
Telangiectasias	61.02%	53.85%	94.74%	9%

Table 9. Sensitivity Analysis of Signs and Symptoms versus Dehydrogenase Lactate (LDH)

	Dehydrogenase Lactate			
Clinical Features	**Sensitivity**	**Specificity**	**PPV**	**NPV**
Adynamia	84.46%	16.67%	78.13%	23.33%
Asthenia	21.23%	85%	83.78%	22.82%
Arthralgias	84.46%	16.67%	78.13%	23.33%
Dry eye	80%	15.29%	10%	86.67%
Eczema	85.8%	25%	86.88%	23.33%
Erythema	85.39%	33.33%	95%	13.33%
Porcelain sclerae	13.04%	78.79%	7.89%	86.67%
Fever	71.43%	14.2%	9.37%	80%
Hair loss	87.5%	16.9%	26.25%	80%
Memory loss	66.67%	14.29%	6.25%	83.33%
Morphea	22.64%	81.25%	61.54%	44.22%
Necrosis	60%	15.14%	1.87%	93.33%
Neurological symptoms	83.81%	15.48%	55.35%	43.33%
Pachydermostosis	85.16%	20%	82.5%	23.33%
Abdominal distension	10.81%	84.96%	32%	59.26%
Photophobia	81.48%	14.81%	27.67%	66.67%
Cutaneous venous dilatations	84.85%	20%	87.5%	16.67%
Dry mouth	80.95%	15.38%	10.63%	86.67%
Headache	84.51%	15.97%	37.5%	63.33%
Hyperacusis	80.39%	12.59%	25.79%	62.96%
Vascular nodules	85.19%	15.95%	14.37%	86.67%
Petechiae	100%	16.22%	3.12%	100%

Table 10. Sensitivity Analysis of Signs and Symptoms versus Lupus Anticoagulant

	Lupus Anticoagulant			
Clinical Features	**Sensitivity**	**Specificity**	**PPV**	**NPV**
Adynamia	85.71%	16.89%	22.64%	80.65%
Asthenia	16.89%	85.71%	80.65%	22.64%
Arthralgias	16.22%	83.33%	77.42%	22.01%
Dry eye	15%	83.53%	10%	89.31%
Eczema	12.96%	64.29%	67.74%	11.32%
Erythema	89.29%	5.66%	14.29%	75%
Porcelain sclerae	8.33%	86.96%	8.69%	86.42%
Fever	9.09%	88.27%	9.52%	87.73%
Hair loss	12.50%	82.39%	19.35%	73.58%
Memory loss	3.70%	91.98%	7.14%	85.14%
Morphea	9%	74.07%	32.26%	36.84%
Necrosis	20%	83.78%	3%	97.48%
Neurological symptoms	12.38%	78.57%	41.94%	41.77%
Pachydermostosis	12.90%	68.57%	64.52%	15.09%
Abdominal distension	32%	59.26%	10.81%	84.96%
Photophobia	16.67%	83.70%	29.03%	71.52%
Telangiectasias	16.38%	84.62%	93.55%	7%
Dry mouth	14.29%	83.43%	10%	88.68%
Headache	11.27%	80.67%	25.81%	60.38%
Myalgia	16%	80%	90.32%	8%

In addition to the aforementioned findings, we found that in some patients, there was an elevation in alkaline phosphatase level, related to the migration of the product to bone or periosteal structures,[16] alteration of glycosylated hemoglobin related to alteration of metabolic pathways,[8] or presence of positive thyroid peroxidase antibodies.[13,14] These aspects have been previously described in other medical conditions of metabolic or autoimmune origin.[18,19] Lactate dehydrogenase is a factor of severity in the behavior of the biopolymer[9–11] and makes it possible to define an early surgical approach, mitigating the symptoms and chronic inflammatory behavior of the disease.[3]

As a limitation of the study, it is considered that a control group was missing to compare and generate the association between immunological markers and human adjuvant disease caused by biopolymer that would allow us to give more power to the diagnostic decision measures. Prospective, analytical studies with epidemiological association are recommended.

CONCLUSIONS

Many of the signs and symptoms described by patients and identified in clinical practice are associated with specific biomarkers involved in immunological processes and can influence the pretest decision to request paraclinicals, improving the diagnostic probability and cost effectiveness. The complex clinical presentation of the biopolymer as well as its pathophysiology makes it a difficult condition to diagnose and treat. This proposal seeks to suggest a tool for the classification of patients created from the natural course of the disease observed and documented in the author's clinical practice. Further research on BHAD should be continued to strengthen the standards of diagnosis, classification, and treatment in such patients and to unify concepts for the common benefit.

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