

Biopolymers: Histopathologic Case Series of Patients with Permanent Synthetic Fillers Presenting Chronic Granulomatous Reaction and Hypercalcemia

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Background: Biopolymers, which are diverse and permanent synthetic fillers, are nonbiocompatible allogeneic materials. Their implantation can result in clinical, radiological, and histopathological manifestations that contribute to our understanding of foreign-body-induced human adjuvant disease.

Methods: We conducted a descriptive observational case series involving 20 patients who underwent open biopolymer removal surgery in the buttocks and lumbosacral regions using the Meticulous Approach Safer and Keeper technique, followed by gluteal reconstruction with autologous tissue. Histopathological analysis was performed. This study was conducted in Bogotá, Colombia, from 2020 to 2023.

Results: Documented clinical records and histopathological analyses of the 20 patients revealed an inflammatory response that was initially considered healthy. Cytoplasmic vacuolization in reactive adipocytes was observed in all cases, meriting consideration in the differential diagnosis of liposarcoma and suggesting local aggressiveness. One patient showed a positive lymphocytic inflammatory response in the Alcian blue test. Hypercalcemia was present in 30% of the patients, elevated lactate dehydrogenase in 40%, and elevated parathyroid hormone levels in 15%.

Conclusions: Surgeons should consider measuring lactate dehydrogenase, serum calcium, and parathyroid hormone levels to assess the severity and guide clinical practice. Secondary prevention through the open surgical removal of biopolymers is recommended. (*Plast Reconstr Surg Glob Open* 2024; 12:e6159; doi: 10.1097/GOX.0000000000006159; Published online 15 October 2024.)

INTRODUCTION

Permanent synthetic fillers, commonly referred to as biopolymers and biomaterials, are nonbiocompatible allogeneic materials with well-documented adverse effects. Consequently, patients who have been exposed to a foreign body and develop local and systemic manifestations, changes in the immunological profile, and radiological findings that are scored and classified according to the Pachón scale can be considered to have foreign body-induced human adjuvant disease.^{1,2} To date, no research has been conducted to prove the association between the presence of a chronic granulomatous reaction and

hypercalcemia secondary to biopolymers. Pachón et al advocated the prompt management of asymptomatic biopolymer carriers to potentially enhance prognosis by ameliorating signs, symptoms, and immunologic markers associated with the disease's natural progression.^{3,4}

This series details the clinical and histopathological observations, providing insight into the adverse reactions engendered by these substances. This study aimed to delineate the clinical, paraclinical, and histopathological profiles of patients who underwent plastic surgery involving biopolymers at a medical facility in Bogotá, Colombia, from 2020 to 2023.

MATERIALS AND METHODS

Design and Setting

A descriptive observational case series was conducted at a plastic surgery clinic in Bogotá, Colombia from 2020 to 2023. This study focused on 20 patients who underwent

Disclosure statements are at the end of this article, following the correspondence information.

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Received for publication March 23, 2024; accepted July 24, 2024.

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DOI: 10.1097/GOX.0000000000006159

open surgery for biopolymer removal using the Meticulous Approach Safer and Keeper (MASK) technique, which also involved gluteal reconstruction with autologous tissues.

Participants

Data were sourced from patients' clinical histories, including pathology reports, laboratory findings, and diagnostic magnetic resonance imaging (MRI) results.

Ethical Considerations

This study adhered to the ethical standards stipulated in Resolution 8430 of 1993 of the Colombian Ministry of Health. Institutional permission to conduct this research was granted by the clinic. Informed consent was obtained from all patients for the use of their clinical images, and the necessary precautions were taken to ensure anonymity.

Data Handling

Clinical and paraclinical data were gathered, processed, and stored by the principal investigator to maintain patient confidentiality. A quantitative approach was used to analyze the data and apply absolute and relative frequency measures to the qualitative variables.

Analytical Methods

Patient data, including the duration of biopolymer presence and associated clinical manifestations, were analyzed using Microsoft Excel 2016. The results are systematically cataloged and graphically presented.

Histopathological Examination

Tissues were fixed in 10% buffered formalin for 24 hours, described macroscopically, and processed in a tissue processor for fixation, dehydration, and clearing, before embedding in paraffin. Histological sections (3 µm) were prepared using a microtome, stained with hematoxylin and eosin and Alcian blue, and examined under an optical microscope.

RESULTS

Description of Cases and Histopathology

Clinical and Paraclinical Findings

Data were collected from 20 patients who underwent histopathological examination after biopolymer removal surgery. Clinical history records indicated the time since biopolymer administration, type of filler used, and positive clinical signs and symptoms, along with preoperative laboratory tests and radiological findings. (See figure, **Supplemental Digital Content 1**, which displays the clinical and paraclinical descriptions of the 20 patients in the case series. <http://links.lww.com/PRSGO/D500>.) The most prevalent symptoms were asthenia (90%), adynamia (85%), myalgia (80%), arthralgia (80%), and somnolence (60%). The most commonly observed clinical signs were morphea (95%), inguinal adenopathy (55%), tissue necrosis (25%), porcelain sclerae (20%), and pachydermatosis (15%).

Takeaways

Question: Is there any relation between severity in biopolymers and hypercalcemia?

Findings: Hypercalcemia was present in 30% of the patients with biopolymers, elevated lactate dehydrogenase in 40%, and elevated parathyroid hormone levels in 25%.

Meaning: The relationship between foreign body (biopolymer)-induced human adjuvant disease and hypercalcemia is explored.

Histopathological Observations

Inflammatory reaction was noted to partially affect tissue previously assessed as healthy in 30% of cases. In case 15, a cystic lesion initially suspected to be synovial metaplasia was later identified as a histiocytic lining due to CD68 positivity, negating the initial hypothesis. Across all cases, reactive adipocytes with cytoplasmic vacuolization were consistently found, prompting consideration of the differential diagnosis of liposarcoma. Molecular studies of murine double minute 2 located on 12q15, also called cyclin-dependent kinase 4 mutations, may be warranted based on clinical, radiological, and histopathological indicators of local aggressiveness, as observed in case 3. A lymphocytic inflammatory response was documented in one patient (case 20), confirmed by positive Alcian blue staining, suggesting the presence of allogeneic material such as acid mucin, proteoglycans, or hyaluronic acid.

Paraclinical Data

In the current series, six patients with preoperative hypercalcemia were documented, with resolution in the first month after surgery and continued negativity throughout the year. Similarly, nine cases with positive lactate dehydrogenase (LDH) before surgery were evidenced, with two cases continuing with elevated values at 1 month of follow-up but with all patients having a negative result at 1 year. Three patients with elevated PTH had negative results at 1 month and 1 year of follow-up.

The series reported hypercalcemia in 30% of patients, elevated LDH levels in 40%, and increased parathyroid hormone levels in 15%. (See figure, **Supplemental Digital Content 2**, which lists preoperative calcium, PTH, and LDH levels and 1- and 12-months follow-up. <http://links.lww.com/PRSGO/D501>.) Clinical progression based on the duration since filler administration was cataloged.

Histopathological Findings

Tissue samples from the cases revealed that the nature of the biopolymer could be related to the observed histopathological changes. (See figure, **Supplemental Digital Content 3**, which displays the histopathological findings for absorbable and permanent synthetic fillers. <http://links.lww.com/PRSGO/D502>.) The four most significant cases out of the total 20 are presented with accompanying images (Figs. 1–6), highlighting the contrast between the affected and unaffected tissues, as well as the granulomatous inflammation and foreign

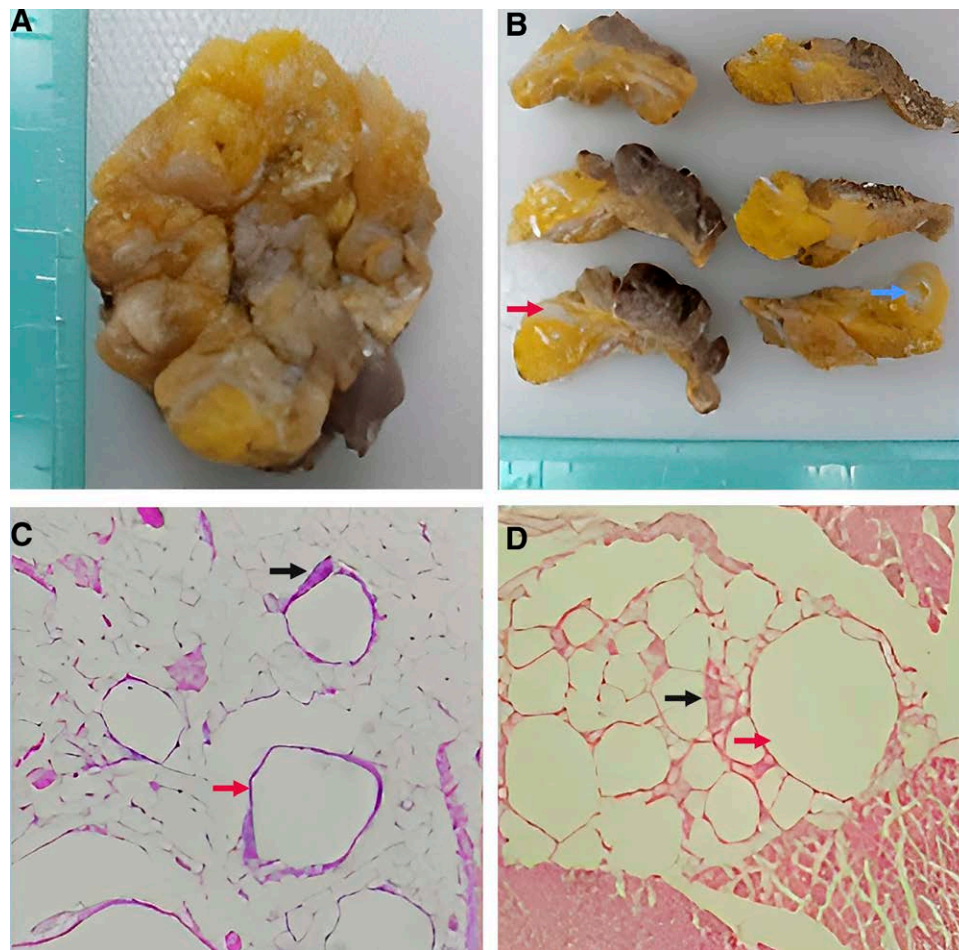


Fig. 1. Case 1: abnormal gluteal tissue. A, Adipose and muscular tissue with infiltration by biopolymers. B, Serial slices. Blue arrow: cavitated lesion with oily content. Red arrow: transparent and shiny oily material. C, Hematoxylin & Eosin (10×): adipose tissue with gigantocellular (black arrow), foreign body (red arrow) reaction. D, Alcian blue (10×): adipose and muscle tissue with inflammatory reaction (black arrow) to a foreign body (red arrow), negative.

body reaction in the context of biopolymer exposure. (See figure, Supplemental Digital Content 4, which displays case 1: undamaged gluteal tissue macroscopic findings. <http://links.lww.com/PRSGO/D503>.) [See figure, Supplemental Digital Content 5, which displays case 1: undamaged gluteal tissue microscopic findings. (10×) <http://links.lww.com/PRSGO/D504>.] (See figure, Supplemental Digital Content 6, which displays case 3: undamaged gluteal tissue macroscopic findings. <http://links.lww.com/PRSGO/D505>.) [See figure, Supplemental Digital Content 7, which displays case 3: undamaged gluteal tissue microscopic findings. (10×) <http://links.lww.com/PRSGO/D506>.] (See figure, Supplemental Digital Content 8, which displays case 15: undamaged gluteal tissue. <http://links.lww.com/PRSGO/D507>.) [See figure, Supplemental Digital Content 9, which displays case 15: muscle and adipose tissue infiltrated by chronic inflammation and foreign body–type gigantocellular inflammation (10×) by allogenic material. <http://links.lww.com/PRSGO/D508>.] [See figure, Supplemental Digital Content 10, which displays case 15: reactive adipocytes

with cytoplasmic vacuolization and irregular nuclei (10×). <http://links.lww.com/PRSGO/D509>.]

DISCUSSION

The use of allogenic materials may lead to cellular reactions as well as granulomatous and antigenic antibody responses, resulting in a range of symptoms, including myalgia, arthralgia, asthenia, adynamia, memory loss, dry eyes and mouth, photophobia, hyperacusis, abdominal distension, neuropathic pain, headache, and hair loss. It is important to note that these symptoms are objective and have been reported in previous studies.^{4,5} In some cases, more severe symptoms, such as loss of consciousness or neurological manifestations of dementia, may also occur.⁶

In previous studies by Pachón et al, the correlation between ASIA syndrome associated with biopolymers was described, along with the clinical and immunological manifestations of patients who underwent surgical removal of the material with an open MASK technique.^{3,4} Furthermore, in 2022, the severity scale for human adjuvant disease caused by biopolymers was published,

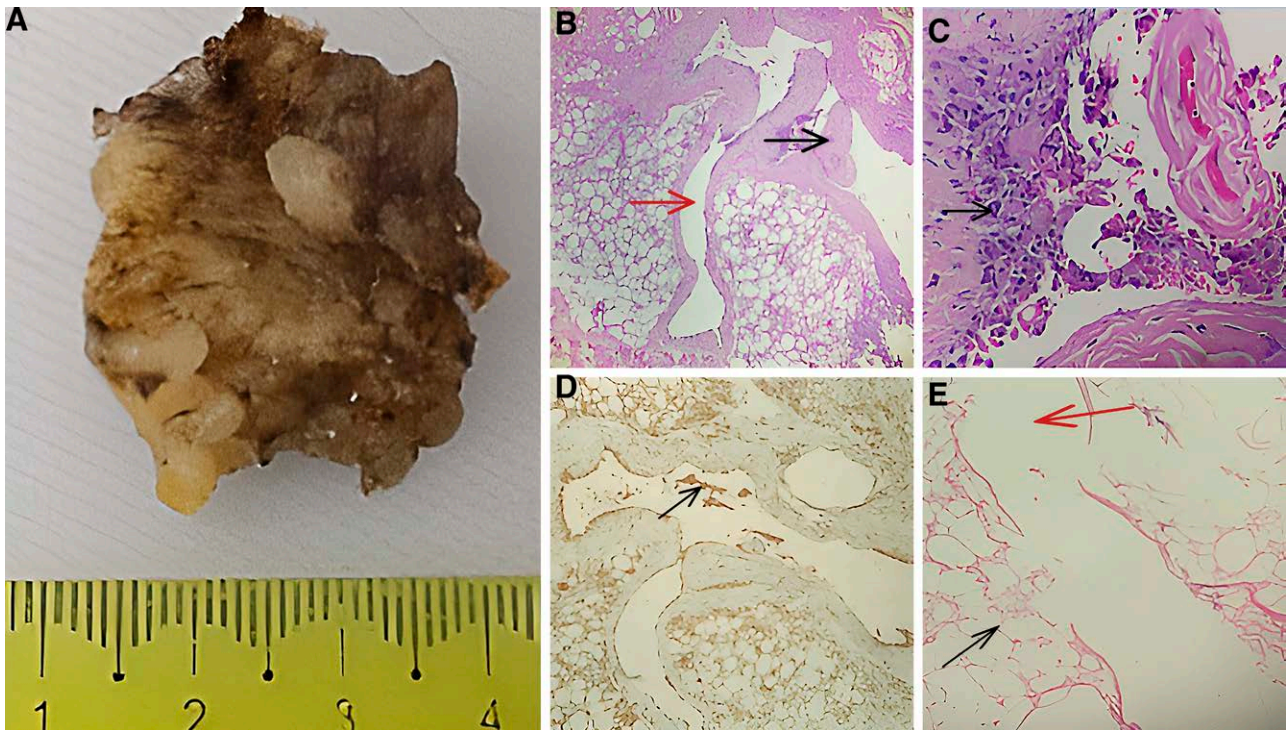


Fig. 2. Case 3: abnormal gluteal tissue. A, The image displays soft tissue affected by biopolymer. B, Hematoxylin and eosin (5×) adipose and muscular tissue with chronic inflammation and foreign body-type giant cells (black arrow), associated with the cavitated area (red arrow). C, Hematoxylin and eosin (40×) chronic inflammation and foreign body-type giant cells (black arrow). D, CD68 is visible and Foamy histiocytes and giant cells (10×) were positively expressed (black arrow). E, Alcian blue coloration (10×) of adipose tissue with an inflammatory reaction (black arrow), negative foreign body staining (red arrow).

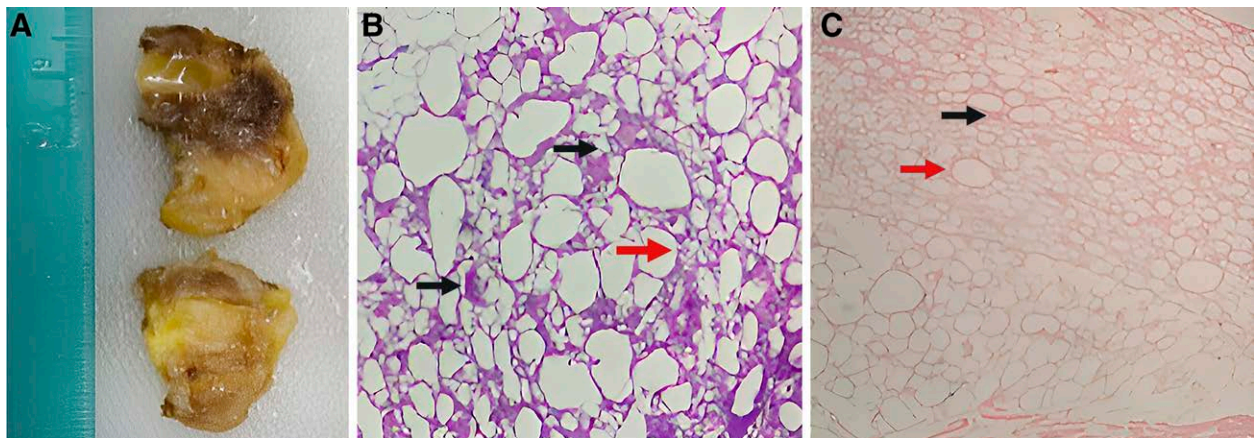


Fig. 3. Case 15: abnormal gluteal tissue. A, Adipose and muscular tissue with cavitation and oily material. B, Histological sections of tissue with lymphohistiocytic inflammation and giantocellular reaction 10× (black arrow), foreign body type to allogeneic material (red arrow). C, Alcian Blue (10×): adipose and muscular tissue with inflammatory reaction (black arrow) to foreign body (red arrow), negative.

demonstrating the sensitivity, specificity, and predictive values of signs and symptoms to guide the diagnostic approach of patients carrying foreign bodies and biopolymers.^{3,4} Macroscopic histopathological findings were also identified and described as light brown adipose tissue. In serial sections, transparent and oily materials can be observed. Histological sections indicated fibromuscular and adipose tissue, as well as a lymphohistiocytic

inflammatory infiltrate. Numerous foreign body-type giant cells contain transparent materials that generate intracytoplasmic vacuoles and displace the nuclei. In patients using allogeneic substances, foreign body-type inflammatory reactions accompanied by varying degrees of lymphohistiocytic inflammation have been observed. The severity of inflammation may be related to the duration of exposure to a substance.⁷

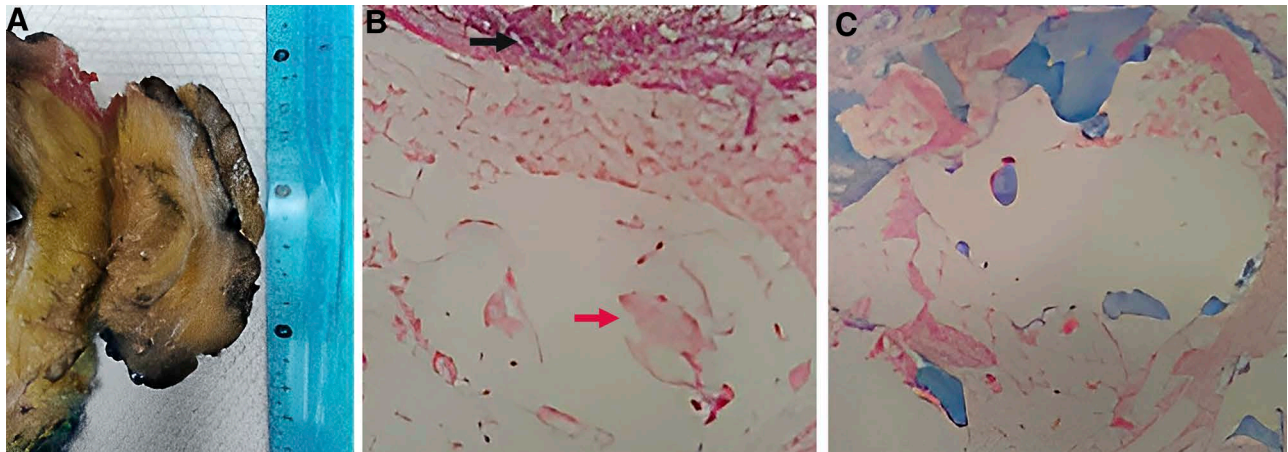


Fig. 4. Histological plates, case 20. A, Macroscopic cut with whitish area and cystic lesion. B, Hematoxylin & Eosin (10×): muscle and adipose tissue infiltrated by refringent material (red arrow) associated with a chronic inflammatory reaction (black arrow). C, Alcian blue (10×): Positive expression in foreign material—allogeneic substance.

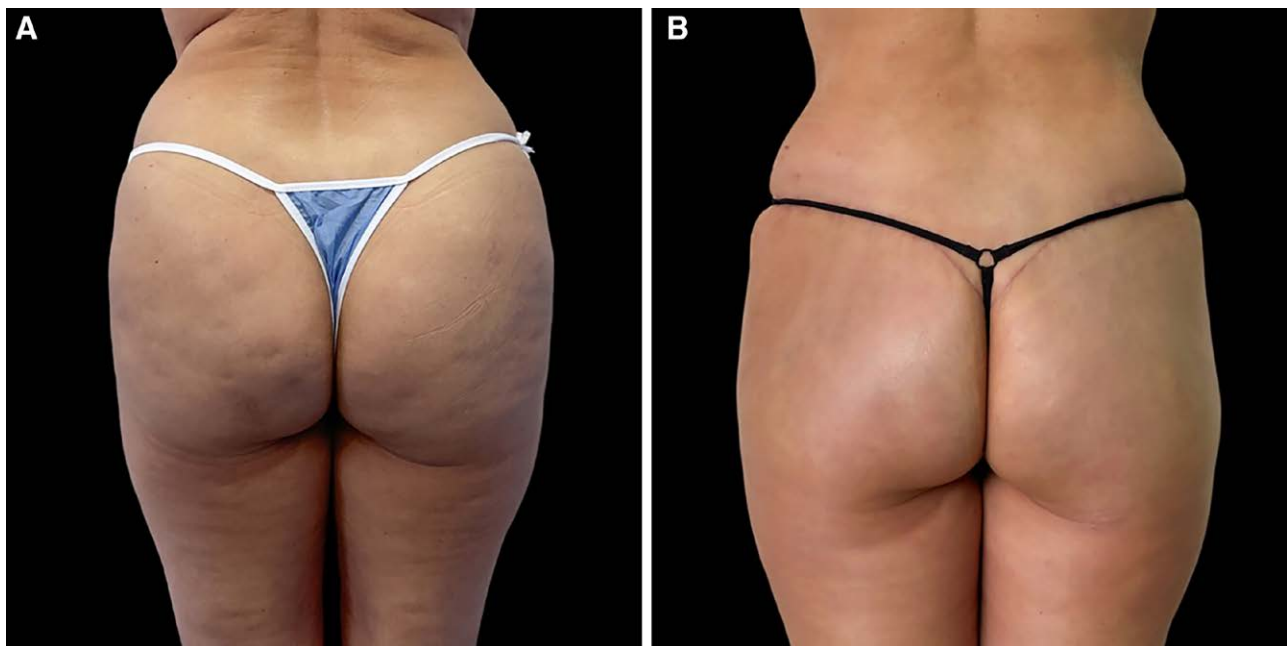


Fig. 5. MASK technique. A, Preoperative result of the MASK technique. B, Postoperative result of the MASK technique.

Previous studies have examined permanent synthetic fillers, which are commonly referred to as biopolymers. Pachón et al published a severity scale that considers local and systemic clinical criteria, radiological criteria, and immunological criteria. It was found that there is a correlation between positive LDH levels and the presence of severe disease caused by biopolymers. The odds ratio was 4.1, with a 95% confidence interval of 1.94–8.92,^{4,5} and established criteria for disease severity.^{6–8} It is therefore recommended that a sample of specimens extracted during surgery from patients with biopolymer implants be sent to the laboratory when the patient shows signs of severity before the procedure, such as changes in serum calcium levels, or when the surgeon observes masses with

changes in consistency and the presence of cavitations and mucinous material content, which suggests the presence of metaplasias or dysplasias. Similarly, the scientific literature has documented the frequency of presentation of elevated levels of parathyroid hormone, LDH, carcinoembryonic antigen, antithyroid peroxidase antibodies, alkaline phosphatase bone fraction, or glycosylated hemoglobin. Therefore, it is recommended to consider these factors for further research that focuses on evaluating the diagnostic and prognostic accuracy at the time of measurement.³

The literature suggests that patients with a lymphocytic inflammatory reaction in hematoxylin-eosin staining in cases of severe metaplasia, evolution to dysplasia,

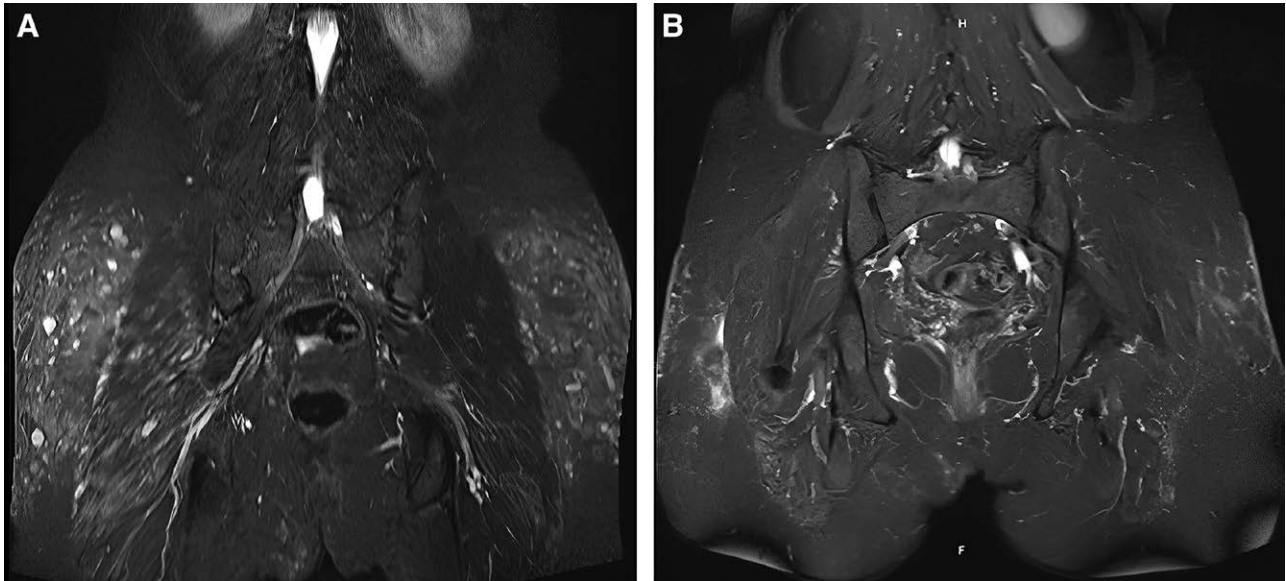


Fig. 6. Pelvic MRI. A, Preoperative nuclear MRI of the pelvis was performed on patient 15 of the series. The presentation was a snowstorm sign and infiltration of the fascia of the gluteus maximus muscle. B, Following the open removal of the biopolymer using the MASK technique, postoperative nuclear MRI of the pelvis was conducted. The results showed a significant reduction in the permanent synthetic filler.

or suspected tumors respond better to chemotherapy^{8,9} Furthermore, the presence of absorbable synthetic filler substances such as hyaluronic acid or D-polylactic acid, or certain types of mucopolysaccharides, can be suspected in individuals with positive basophilic expression in alcianophilic material. This association has been described with benign pathologies, such as mucocèles, and malignant pathologies, such as adenocarcinomas or myxomas.^{5,10,11} However, in this series, the pathology of case 20 was negative for these types of products and malignancies

It is crucial to obtain comprehensive information from the anamnesis documented in the patient's medical history before the surgical procedure. This enables the pathologist to perform an adequate clinicopathological examination and to distinguish between reactive adipocytes compromised by synthetic material and lipoblasts in the absence of an inflammatory response, as well as to differentiate between a history of substance application and the absence thereof.^{11,12}

This study documented preoperative serum calcium elevation in six of 20 patients. This elevation may be related to the exposure of permanent synthetic filler material (biopolymer), which generates extrarenal production of 1,25-hydroxyvitamin D₃. The literature describes situations such as hypercalcemia associated with granulomatous diseases, with sarcoidosis or tuberculosis being the most frequent.^{13–15} These situations share similarities with type IV hypersensitivity reactions, as observed with biopolymers, which are related to the overexpression of the vitamin D receptor and the enzyme alpha 1 hydroxylase.¹⁶ This enzyme activity results in overproduction of calcitriol, which increases the absorption of dietary calcium in the intestines. This in turn leads to osteoclastic activity and increased bone reabsorption, resulting in elevated calcium levels.¹⁷

Ninety-eight percent of calcium is present in the form of hydroxyapatite in bones, whereas only 1% is found in the extracellular fluid. Serum calcium concentrations are regulated by hormones, such as calcitonin or parathyroid hormone, which are in turn regulated by phosphorus and magnesium.^{8,9} Although the systemic effects of hypercalcemia typically require levels of more than 12 mg per dL, some symptoms can still occur at lower levels. These symptoms included asthenia, adynamia, irritability, psychosis, depression, weakness, and cognitive alterations. Pachón et al^{3,4} previously linked these symptoms to the administration of biopolymers.

Arterial hypertension is a common finding along with manifestations such as constipation, abdominal pain, and polyuria. Hyperparathyroidism, renal calculi, fractures due to osteoporosis, bone deformities, and conjunctivitis were described in this series.^{5,10,18,19} In permanent synthetic fillings, granulomatous conditions can be objectively measured by identifying an elevation of 1,25-hydroxyvitamin D₃ by macrophages inside the granulomas. Therefore, it is important to evaluate hypercalciuria earlier than hypercalcemia. This is because serum calcium is regulated by parathyroid hormone, although the indirect production of 1,25-dihydroxyvitamin D is mediated by macrophage activity at the time of granuloma formation. The greater the phagocytosis of adjuvant, the greater the amount of 1,25-dihydroxyvitamin D. This is then transported into the serum, where it stimulates the activity of calbindin at the gastric level. This, in turn, favors the production of alpha 1 hydroxylase, which has a direct effect on the kidney, causing calcium excretion (hypercalciuria) and calcium reabsorption in the distal and collecting tubules (hypercalcemia).^{17,20,21}

It is well known that these patients do not benefit from treatment with recombinant enzymes such as

hyaluronidase, collagenase, lyase, or lipase; they only benefit from open biopolymer removal, and as an expert, I recommend the MASK technique [Figure 5](#). Medical treatment should begin with intravascular volume repletion, which should be quantified by measuring the number of fluids administered and eliminated as well as the renal excretion of calcium. It is essential to consider ASA diuretics, such as furosemide, but to be cautious about hypokalemia and secondary hypomagnesemia.^{21,22} In severe cases, complementary pharmacological measures such as corticosteroids (oral prednisolone 20–40 mg/day for 5–7 days), ketoconazole, or infliximab may be evaluated to inhibit the action of alpha 1 hydroxylase.^{23,24}

The histopathological correlation of chronic granulomatous disease allows us to understand and explain the pathophysiological aspects related to the local and systemic symptomatology of the case series of our patients. However, the histopathological description in this article aims to identify common histological phenomena in patients with biopolymers, such as lymphohistiocytic inflammatory infiltrate with foreign body–type giant cells. Additionally, there is a suspicion of metaplastic processes that require further study in different patient specimens exposed to permanent synthetic fillers. In this context, it is important to perform a histopathological study of all patients who carry allogeneic substances with altered immunological markers, hypercalcemia, LDH (+), or elevated parathormone levels. This study should take into consideration the differential diagnosis of mesenchymal neoplasms, such as liposarcoma and granulomatous diseases, with the understanding that the presence of this substance with its associated inflammation does not exclude them.^{24–26}

Another possible diagnosis is sarcoidosis. Therefore, clinical practice should include the search for pulmonary, lymph node, ocular, hepatic, cardiac, bone, central nervous system, and cutaneous involvements. Pachón et al previously conducted studies on the use of preand postoperative carcinoembryonic antigens to monitor patients with biopolymers. A positive correlation was found in two of the 190 patients studied, which may be related to hypercalcemia and sarcoidosis-like clinical features.^{3,4,24} Although complete removal of permanent synthetic fillers is not possible, removing them as much as possible can improve the quality of life. This has been documented by the improvement of postoperative symptoms one year after surgery, as well as preoperative and postoperative simple nuclear magnetic resonance of the affected area, and postoperative one year after surgery. Please refer to [Figure 6](#).

CONCLUSIONS

The study indicated that LDH was positive in 40% of cases, hypercalcemia in 30%, and parathyroid hormone levels were elevated in 15%. In addition, a chronic inflammatory reaction with a gigantocellular foreign body reaction was observed. Hypercalcemia may be related to excessive amounts of absorbable and permanent synthetic fillers (biopolymers) and immunological activity generated by the histopathological formation of granulomas.

Therefore, it is important to consider this finding from a pathophysiological perspective. Positive basophilic expression in cyanophilic material is typically present in patients with absorbable synthetic fillers, such as hyaluronic acid or D-poly-lactic acid.

Patients with biopolymer and elevated LDH levels showed increased preoperative serum calcium levels. Furthermore, histopathological analysis revealed an association between multinucleated giant cells, abundant lymphohistiocytic infiltrates, and giant cells containing clear material with intracytoplasmic vacuoles (permanent synthetic filler). Currently, there is no conclusive evidence to support routine requests for serum calcium and parathyroid hormone levels before surgery. However, in this case series, some patients had elevated levels before undergoing surgery. Therefore, further research in this area is required to improve this evidence. If the markers and LDH are positive, samples should be collected intraoperatively for histopathological studies to determine changes related to histological severity, such as metaplasia or dysplasia. This may be an eventual finding in the natural history of a foreign body (biopolymer)–induced human adjuvant disease.

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

ACKNOWLEDGMENT

We would like to thank the Pathology Center of the Colsanitas Clinical Laboratory in Bogotá Colombia for their collaboration in the histological processing of the samples.

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