

Peer Review File

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Reviewer A

Comment 1: Very interesting case, I don't have any experience with complications from PAAG, but I would generally assume that they are caused by infection, but is that not the case?

Reply 1: Thanks for your kind questions. PAAG injections can cause short-term and long-term adverse reactions. Typical early complications of polyacrylamide hydrogel injection are lumps, hematomas, and infections. Christensen et al. revealed bacteria were identified in bacteriologically investigated samples (98%) from the patients with adverse reactions to polyacrylamide gel, even up to 5 years postinjection. [Christensen L, Breiting V, Bjarnsholt T, et al. Bacterial infection as a likely cause of adverse reactions to polyacrylamide hydrogel fillers in cosmetic surgery. Clin Infect Dis 2013;56:1438-44.] However, the microbiological culture of pus and PAAG was negative upon examination for pathogens.

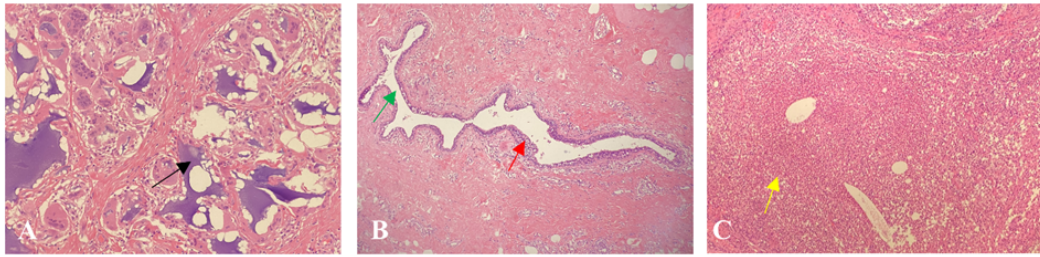
The patient in our study suffered from a 8-month history of a painful and swollen mass in her left breast in 2021, and previously had a cosmetic intervention of PAAG injection for breast augmentation in 2010 and subsequently underwent PAAG removal operation in 2011. Pathological examination of the surgical specimen revealed foreign-body granulomas caused by residual granular PAAG and microabscesses formation. Therefore, on the basis of clinical complaints, cosmetic history, and histopathological results and our experience, the complication of this reported case was long-term granulomatous mastitis. Specially, the patient complained of left upper extremity numbness and we observed pectoralis major muscle defect intraoperatively. So, we indicated that our case were not caused by infection, but long-term granuloma.

Changes in the text: we have modified our text as advised (see Page 3, line 107-108; Page 4, line 130-132; Page 4, line 148-151; Page 5, line 179-183) .

Comment 2: It seems unlikely that a granulomatous mammary line is the pathology, but is granulomatous mastitis a background pathology in past reviews?

Reply 2: Thanks for your kind question. According to the literature, one of the primary long-term problems is characterized by the foreign-body granulomatous mastitis caused by PAAG. [Ono S, Ogawa R, Hyakusoku H. Complications after polyacrylamide hydrogel injection for soft-tissue augmentation. Plast Reconstr Surg 2010;126:1349-57.] We performed an incisional biopsy for pathological confirmation with foreign-body granulomas caused by residual granular PAAG and microabscesses formation. We have added the histopathologic patterns of granulomas in Figure 3C (yellow arrow).

Changes in the text: we have modified our text as advised (see Page 4, line 130-132; Page 5, line 179-183) and Figure 3.



Comment 3: It seems that the patient was treated with antibiotics, but there was little improvement, and the length of the 8-month waiting period did not lead to the loss of the pectoralis major muscle?

Reply 3: Thanks for your kind question. The patient developed a palpable mass with bursting pain and swelling in her left breast, and was diagnosed with mastitis by a core needle biopsy and treated with antibiotic therapy ineffectively in May 2020, at another institution. After 7-month self-observation, she suffered from progressive local and general symptoms, and was admitted to our department. She didn't undergo ultrasound and MRI imaging examination before, so we can't judge the damage of pectoralis major muscle compared to our imaging results.

Our department, as a center dealing with granulomatous mastitis patients intensively from local and out-of-town regions, has encountered over 3,000 patients in the last 10 years, and over 1,000 of these patients underwent a surgical operation; however, we never found that granulomatous mastitis would damage the structure of pectoralis major muscle.

According to the literature, as a foreign body, PAAG can form a fibrous capsule within a pseudocapsule, and damage the structure of the pectoralis major muscle and extrapleural space. Yang Y et al. reported that PAAG gel diffused into the pectoralis major and minor muscles of 70.93% patients and intercostal muscles of 2.33% patients. So we indicated that the loss of the pectoralis major muscle was stimulated by the residual PAAG and chronic granulomatous mastitis. [Margolis NE, Bassiri-Tehrani B, Chhor C, et al. Polyacrylamide gel breast augmentation: report of two cases and review of the literature. Clin Imaging 2015;39:339-43. Yang Y, Li S, He J, et al. Clinicopathological Analysis of 90 Cases of Polyacrylamide Hydrogel Injection for Breast Augmentation Including 2 Cases Followed by Breast Cancer. Breast Care (Basel) 2020;15:38-43.]

Changes in the text: we have modified our text as advised (see Page 4, line 121-124; Page 5, line 160-165).

Comment 4: The image should show an arrow to the lesion.

Reply 4: Thanks for your kind suggestion. We presented different parts using different color arrow.

Changes in the text: we have modified our figures as advised (see figure 1-3).

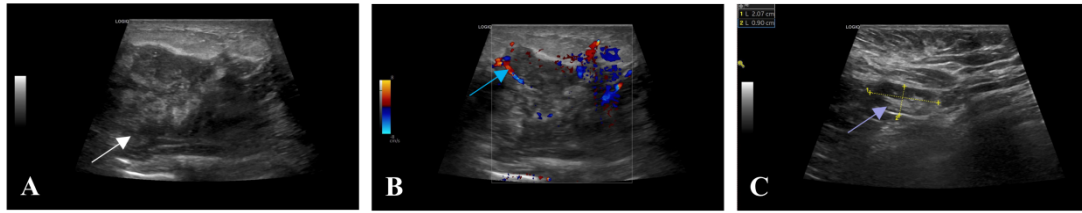


Figure 1. Ultrasound images. (A) Left-breast grayscale ultrasound images demonstrating a heterogeneous lesion (white arrow), (B) Left-breast Color Doppler Flow Imaging (blue arrow), (C) Enlarged lymph nodes in the left axilla (purple arrow).

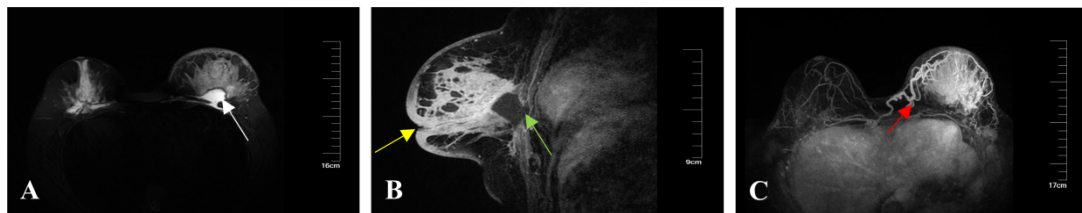


Figure 2. MRI images. (A) Axial T2-weighted images showing PAAG granules with hyperintensity (white arrow), (B) Enhanced sagittal T1-weighted images showing nipple retraction, skin thickening, peripheral edema (yellow arrow), and partial defect of the pectoralis major muscle (green arrow), (C) Enlarged and circuitous blood vessels around the lesions (red arrow).

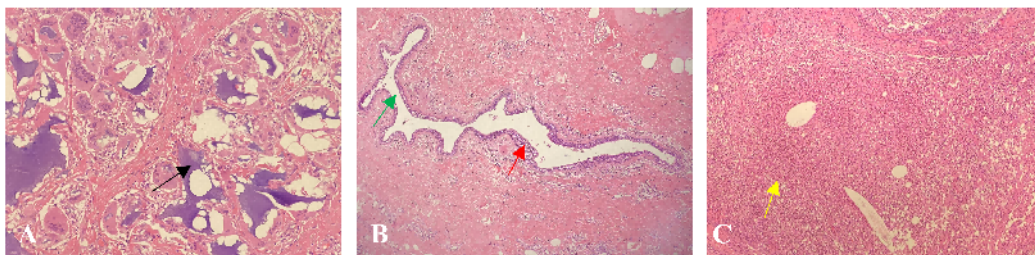


Figure 3. Histopathologic images (H&E staining, ×200). (A) Residual gel-like granular PAAG (black arrow), (B) Dilated ducts (green arrow) with infiltrative lymphocytes, plasma cells, and neutrophils (red arrow), (C) Foreign-body granulomas and microabscesses (yellow arrow).

Comment 5: I think the references are generally outdated. This may be due to the lack of recent reports, but if so, the report seems to have little value.

Reply 5: [Thanks for your kind suggestion and we have updated the references.](#)

[Changes in the text: we have modified our references as advised \(see Page 7\).](#)

Comment 6: In conclusion, PAAG for augmentation mammoplasty carries the risk of breast mass development, migration, infection, and pectoral muscle injury. It states that this is a known fact and that is why its use is prohibited. I think the discussion should include more details about the treatment. For example, is surgery mandatory? If so,

shouldn't surgery be performed as early as suspected?

Reply 6: Thanks for your kind suggestion. As the literature and our case has shown, PAAG filler complications are often permanent and difficult to treat, and improper management of complications usually results in further secondary damage. Considering the severity of the complications caused by PAAG injection, it is worth mentioning that adverse reactions should be carefully monitored and catalogued. In some cases with lumps at circumscribed one site, fine needle aspiration or an open procedure involving a small incision can be useful for removing the material. However, injected PAAG is likely to diffuse in layers and result in secondary inflammation, so the complete removal is extremely challenging. When conservative procedures fail, long-term granuloma-related complications were recommended to be treated by surgical intervention. When determining how to perform appropriate operation methods, Jin R et al. developed a surgical management protocol based on a practical classification guideline for patients with PAAG-injected breast augmentation. [Jin R, Luo X, Wang X, et al. Complications and Treatment Strategy After Breast Augmentation by Polyacrylamide Hydrogel Injection: Summary of 10-Year Clinical Experience. Aesthetic Plast Surg 2018;42:402-9. Ono S, Ogawa R, Hyakusoku H. Complications after polyacrylamide hydrogel injection for soft-tissue augmentation. Plast Reconstr Surg 2010;126:1349-57. Cheng NX, Xu SL, Deng H, et al. Migration of implants: a problem with injectable polyacrylamide gel in aesthetic plastic surgery. Aesthetic Plast Surg 2006;30:215-25. Christensen L, Breiting V, Bjarnsholt T, et al. Bacterial infection as a likely cause of adverse reactions to polyacrylamide hydrogel fillers in cosmetic surgery. Clin Infect Dis 2013;56:1438-44.]

From our perspectives, we recommended all patients were routinely examined by ultrasound and enhanced MRI to assess the extent of the lesion preoperatively. For lumps with no local inflammatory manifestations, encapsulated gel material may be easily removed by fine needle aspiration or open surgery with small incisions; whereas chronic inflammation is present, surgical intervention is considered a preferred modality for management.

Changes in the text: we have modified our text as advised (see Page 5-6, line 166-207).

Besides, after comprehensive consideration, we changed **the title** to "Granulomatous mastitis and pectoralis major muscle defect following polyacrylamide hydrogel injection: A case report and literature review".

Reviewer B

Comment 1: Please provide the full name of "PAAG" in the highlight box.

Reply 1: Thanks for your kind suggestion. We have corrected the text in the highlight box as Polyacrylamide hydrogel (PAAG) in line 65.

Comment 2: Please indicate the full name of "BI-RADS 4A" in the abstract and the main text.

Reply 2: Thanks for your kind suggestion. We have indicated the full name of "BI-

RADS 4A” as Breast Imaging - Reporting and Data System 4A (BI-RADS 4A) in the abstract in line 49-50 and the main text in line 116-117.

Comment 3: Figures

- 1) The citation of Figure 3 is missing in the text. Please check and revise.
- 2) Please check through and make sure that **all abbreviations in each figure and table have been defined in each legend**. For example, please provide the full names of “PAAG” in the legend of **Figures 2-3**.

Reply 3: Thanks for your kind comments. We have revised the citation of Figure 4 (after reversion) in line 132 and defined all abbreviation in each legend of the figures in **Legends** section.

Comment 4: The author’s name is inconsistent with the corresponding reference. Please check and revise.

- **Chen G et al.** (11) presented a case of malignant breast tumor development following PAAG breast augmentation, demonstrating the possible correlation between PAAG injection and breast malignancy.
 11. **Zhao Y, Yuan NA, Li K, et al.** Bilateral breast cancer following augmentation mammoplasty with polyacrylamide hydrogel injection: A case report. *Oncol Lett* 2015;9:2687-93.
- **Ewa et al.** (7) concluded that the patients diagnosed with autoimmune syndrome induced by adjuvants (ASIA), ...
 7. **Woźniak-Roszkowska E, Maślińska M, Gierej P, et al.** Autoimmune syndrome induced by adjuvants after breast enhancement with polyacrylamide hydrogel: a study in Poland. *Rheumatol Int* 2020;40:1851-6.

Reply 4: Thanks for your kind comment. We were sorry for the mistakes and have corrected the author name of the corresponding reference 7 in line 157 and reference 11 in line 189.