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Safety of Copolyamide Filler Injection for Breast Augmentation

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Background: Although injections with copolyamide fillers (Aquafilling/Los Deline and Aqualift/Activegel) are currently used widely for breast augmentation, many complications have been reported. A recent position statement by a Korean aesthetic/reconstructive breast surgery society indicated these fillers are the same as polyacrylamide gel (PAAG), which is widely prohibited due to complications. To test this statement, this retrospective cohort study examined the clinical complications after breast augmentation with copolyamide fillers. Nuclear magnetic resonance (NMR) analysis of copolymer and PAAG fillers was also conducted.

Methods: All consecutive patients with concerns about or sequelae from copolyamide fillers who visited our hospital in 2018–2020 were identified. The injected formulation, complications, and intraoperative findings were recorded. Copolyamide fillers were compared with PAAG and 2 PAAG fillers (Amazingel and Aquamid) by NMR.

Results: Of the 29 patients (all women; average age, 42 years), 17 complained of breast deformity. Eight had puncture site infections and mammary gland inflammation. Five exhibited induration (single large/small lumps). In 4 cases, the filler had migrated outside of the breast, including to the back and vulva; these cases had severe symptoms. NMR showed that the copolyamide and PAAG fillers bore all of the characteristic peaks of PAAG.

Conclusions: Our clinical/intraoperative and NMR findings showed, respectively, that copolyamide fillers cause the same complications as PAAG fillers and have the same composition. Thus, the risks of copolyamide fillers for breast augmentation are equivalent to those for PAAG fillers. It is strongly recommended not to use copolyamide fillers until their long-term safety is established. *(Plast Reconstr Surg Glob Open 2021;9:e3296; doi: 10.1097/GOX.0000000000003296; Published online 17 February 2021.)*

INTRODUCTION

Aquafilling (Biomedica, spol, s.r.o., Czech Republic) is a hydrophilic gel that is composed of 98% sodium chloride solution (0.9%) and 2% copolyamide. It was developed for facial contouring in the Czech Republic in 2005.[1] Since 2018, the same product has been sold under the name Los Deline (Bio Trh, s.r.o., Czech Republic). Aqualift (National Medical Technologies Center Co., Ltd., Ukraine) is a similar formulation that was first copyrighted in 2013 and then renamed to Activegel in 2015. It is also composed of 98% sodium chloride solution (0.9%) and 2% copolyamide.

Shin et al[2] have reported that Aquafilling/Los Deline injections effectively correct mild unfavorable results after breast augmentation with silicone implants. Single large-volume injections for breast augmentation are now employed all over the world, including Europe, Japan, and Korea.

However, the safety of these products remains controversial because sequelae after these injections have been reported by multiple case reports.[1,3–7] These sequelae include mastalgia, gel migration, inflammation, infection, and nodular lesions[1,3–7] and are believed to be due to the copolyamide. Concern about these products led the President of the Korean Academic Society of Aesthetic and Reconstructive Breast Surgery to state in 2016 that the copolyamide in at least Aquafilling/Los Deline is poly(acrylamide-co-N,N′-methy-lene-bisacrylamide), as

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indicated by the documents submitted by Biomedica to the Korean Food and Drug Administration.[8] This means that the copolyamide has the same composition as polyacrylamide gel (PAAG) fillers, which have been reported to have serious adverse complications when used for breast augmentation, including localized lumps, deformities, infections, gel migration, and loss of the ability to breastfeed. As a result, the President expressed significant concerns about the safety of Aquafilling/Los Deline and opposed its use for breast augmentation until it has been shown to be safe over the long term.[8]

Despite this position statement, the similarities and differences between the copolyamide fillers (ie, Aquafilling/Los Deline and Aqualift/Activegel) and PAAG fillers in terms of complications have never been formally examined. At Nippon Medical School in Tokyo, Japan, we have an outpatient clinic that specializes in sequelae after cosmetic surgery. As a result, we have extensive therapeutic experience with the aftereffects of PAAG fillers, including Aquamid (Contura International A/S, Denmark) and Amazingel (NanFeng Medical Science and Technology Development Co., Ltd., Shijiazhuang, People's Republic of China).[9] In this article, we report the commonalities and differences between conventional PAAG fillers and the copolyamide fillers by retrospectively analyzing the findings of all patients who presented with sequelae from copolyamide filler breast augmentation over a 27-month period in 2018–2020. We also determined the composition of all filler products by nuclear magnetic resonance (NMR) analysis.

MATERIALS AND METHODS

Retrospective Cohort Study

This retrospective cohort study was conducted on all consecutive patients who had undergone breast augmentation injections with copolyamide fillers and who visited our hospital during the 27-month period between January 2018 and March 2020 due to injection sequelae or concerns. The age, sex, formulation that was used, the sequelae, and their treatment were extracted from the medical records.

NMR Analysis of Copolyamide and PAAG Fillers

The components of Aquafilling/Los Deline and Aqualift/Activegel were analyzed by NMR spectroscopy (the formulations actually tested bore the labels Los Deline and Aqualift). The data were processed by using Alice2 for windows, ver.6 (JEOL DATUM Ltd., Tokyo, Japan) and were compared with the existing data in our in-house NMR database for PAAG itself and 3 additional formulations of PAAG, namely, the Amazingel and Aquamid fillers and the precast polyacrylamide gel e-PAGEL HR that is used for electrophoresis (EHR-T 7.5L, ATTO Corporation, Japan). The NMR data of the latter 3 products and the 2 copolyamide fillers were all obtained with the same procedure. Thus, each product was injected into a 3.2-mm (outer diameter) sealing sample tube (JEOL Ltd., Tokyo, Japan), and Field Gradient Magic Angle Spinning (FGMAS) or solution-state NMR analyses were performed at a proton frequency of 500 MHz (11.7 tesla) using a JNM-ECZ500R (JEOL Ltd.) interfaced with a 3.2-m FGMAS probe at room temperature under the conditions shown in Table 1.

RESULTS

Patient and Copolyamide Filler Injection Characteristics

In total, 29 patients presented to our hospital during the 27-month study period. Their details are shown in Table 2. All patients were female and their average age was 42 (range, 26–61) years. According to the patients, 1 received both Aquafilling/Los Deline and Aqualift/Activegel (these formulations were called Aquafilling and Aqualift); 24 received Aquafilling/Los Deline (23 with the formulation called Aquafilling and 1 with the formulation called Los Deline); and 5 received Aqualift/Activegel (3 with the formulation called Aqualift and 2 with the formulation called Activegel).

The average injected volume was 141.03 (20–250) g for the left breast and 138.96 (0–250) g for the right breast [note that 1 patient (case 1) received a volume of 0 in her right breast; this indicates that only the left breast was treated]. The average duration between receiving the injection(s) and coming to our hospital was 22.1 (0.5–48) months.

Copolyamide Filler Complications

Three patients reported having hypochondralgia, pain/discomfort, and chronic pain at presentation 34, 38, and 33 months after the infusion, respectively. Seventeen of the 29 cases (59%) complained of breast deformity. There were 8 cases of infection (28%). In all cases, local infection at the puncture site and inflammation had spread to the whole mammary gland. Induration was seen in 5 cases (17%) and varied from single large to small lumps. Migration of the filler outside of the breast was rare (4/29, 14%), but these cases had the worst symptoms. In

Table 1. Conditions Used to Obtain NMR Spectral Data for the 2 Copolyamide Fillers and the 4 Forms of Polyacrylamide

NMR Parameters*	
NMR equipment	JNM-ECZ500R (JEOL Ltd., Tokyo, Japan)
^{1}H resonance frequency	500 MHz
Field strength	11.7 tesla
Method	FGMAS
Temperature	Room temperature (22.2–22.8°C)
Magic angle spinning speed	5 kHz
Sample tube	φ3.2-mm sealing sample tube (JEOL Ltd.)
Sample volume	≒47 μL
Sequence	Single pulse
Radiofrequency pulse width	2.05 μs
Relaxation delay	5.0 s
Acquisition time	1.74588 s
Repetition time	6.74588 s
Spectral width	9384.38 Hz
Data points	16,384
Transients	8

*Except for the e-PAFEL HR polyacrylamide product, the strong signal arising from the free water was suppressed by using DANTE presaturation.

Table 2. Patient Demographics, Treatment Details, Sequelae Observed at Presentation to Our Hospital, and Imaging and Treatments Performed at Our Hospital

Case	Age (y)	Sex	Product	Volume Injected in Breast (g)	Volume Injected in the Right Breast (g)	Period from Consultation to Injection (mo)	Deformity	Migration Out of the Breast	Infection	Induration	Other	Scan	Treatment in Our Hospital
1	43	F	Aqualift	20	0	15	○						FU
2	34	F	Activegel	200	200	33	○					CT	Surgery
3	29	F	Aqualift	50	50	30	○	○				CT	Surgery
4	43	F	Aqualift	200	200	1	○						FU
5	26	F	Aquafilling Aqualift	100	100	23		○	○				Surgery
6	49	F	Aquafilling	200	200	10	○						Surgery
7	51	F	Aquafilling	100	100	15					Worried but no symptoms	MRI	FU
8	32	F	Aquafilling	100	80	3			○			CT	Cons. Ttmt
9	48	F	Aquafilling	200	200	24	○		○			CT	Surgery
10	45	F	Aquafilling	100	100	12					Worried but no symptoms	CT	FU
11	28	F	Aquafilling	100	100	46	○			○		CT	Surgery
12	61	F	Aquafilling	150	150	30	○						Surgery
13	44	F	Aquafilling	220	200	47	○					CT	Surgery
14	48	F	Aquafilling	50	80	2					Worried but no symptoms	CT	FU
15	43	F	Aquafilling	100	100	40					Worried but no symptoms	CT	FU
16	35	F	Aquafilling	200	150	0.5			○			CT	Surgery
17	38	F	Aquafilling	100	100	5			○			CT	Surgery
18	32	F	Aquafilling	200	200	34	○	○			Hypochondralgia	CT	Surgery
19	61	F	Aquafilling	100	100	20	○			○		CT	Surgery
20	44	F	Aquafilling	180	200	10	○					CT	FU
21	34	F	Aquafilling	200	200	7					Worried but no symptoms	CT	FU
22	38	F	Aquafilling	100	100	48	○		○			CT	Surgery
23	55	F	Aquafilling	200	200	12					Worried but no symptoms	CT	FU
24	43	F	Los Deline	250	250	45	○	○	○			CT	FU
25	49	F	Aquafilling	100	100	3					Worried but no symptoms	CT	FU
26	32	F	Aquafilling	120	120	47	○		○	○	Hematoma	CT、MRI	
27	54	F	Aquafilling	200	200	38	○			○	Chronic pain	CT	
28	50	F	Aquafilling	100	100	33					Pain, uncomfortable feeling	CT	
29	36	F	Activegel	150	150	6	○			○		CT	

Cons. Ttmt, conservative treatment; F, female; FU, follow-up; MRI, magnetic resonance imaging.

these 4 cases, the filler had migrated to the back and vulva. Seven patients (24%) were asymptomatic but came to our hospital because they had become concerned after hearing a news report that discussed the joint statement of 4 Japanese aesthetic medicine-related societies that called for careful use of Aquafilling/Los Deline.

Treatments Provided in Our Center

We conducted imaging scans in 24 patients (83%): computed tomography (CT) scans were performed in 22 cases and magnetic resonance imaging was performed in the remaining 2 cases. Surgery was performed in 13 cases (45%), 11 patients (38%) were monitored by follow-up, and 1 patient was given conservative treatment.

NMR Analysis of Copolyamide and PAAG Fillers

NMR spectra were obtained for the 2 copolyamide fillers and compared with reference spectral data for PAAG, 2 PAAG fillers (Aquamid and Amazingel), and a commercial PAAG electrophoresis gel (e-PAGEL HR) (Fig. 1). The 4 characteristic peaks of PAAG shown by the gray ranges were present in all fillers and the electrophoresis gel. Thus, the copolyamide fillers Aquafilling/Los Deline and Aqualift/Activegel appear to be similar to PAAG and PAAG fillers in terms of composition.

Physical Appearance of Copolyamide Filler after Desiccation

When collecting the copolyamide filler samples for the NMR study, a fresh formulation of Aqualift 50 g was opened to extract 1 mL. The bag with 49 g of product was then left open to the air and stored in its box in a room at room temperature for about 3 months. At that point, the components had solidified into a hard resin due to evaporation of the water in the bag (Fig. 2). When the weight of the material was measured, it was only 1.19 g.

CASE REPORTS

Case 2

This 35-year-old woman underwent injections with 200 g of Aqualift/Activegel into both the left and right breasts about 3 years ago. Immediately after the injection, she developed infectious symptoms and the doctor who had performed the injections irrigated the injection sites. Three months later, another doctor performed cannula lavage from the axilla but could not remove all of the filler. By the time the patient visited our hospital, preoperative CT revealed widespread persistence of Activegel under the left and right mammary glands and under the pectoralis major muscle (Fig. 3A). The filler had invaded the pectoralis major muscle fibers and had spread to the space under the pectoralis major muscle (Fig. 3B, C). The filler was removed as much as possible. The postoperative course was favorable and a follow-up CT confirmed marked improvement.

Case 5

This 26-year-old woman underwent injections with 100 g of Aquafilling/Los Deline into both the left and right

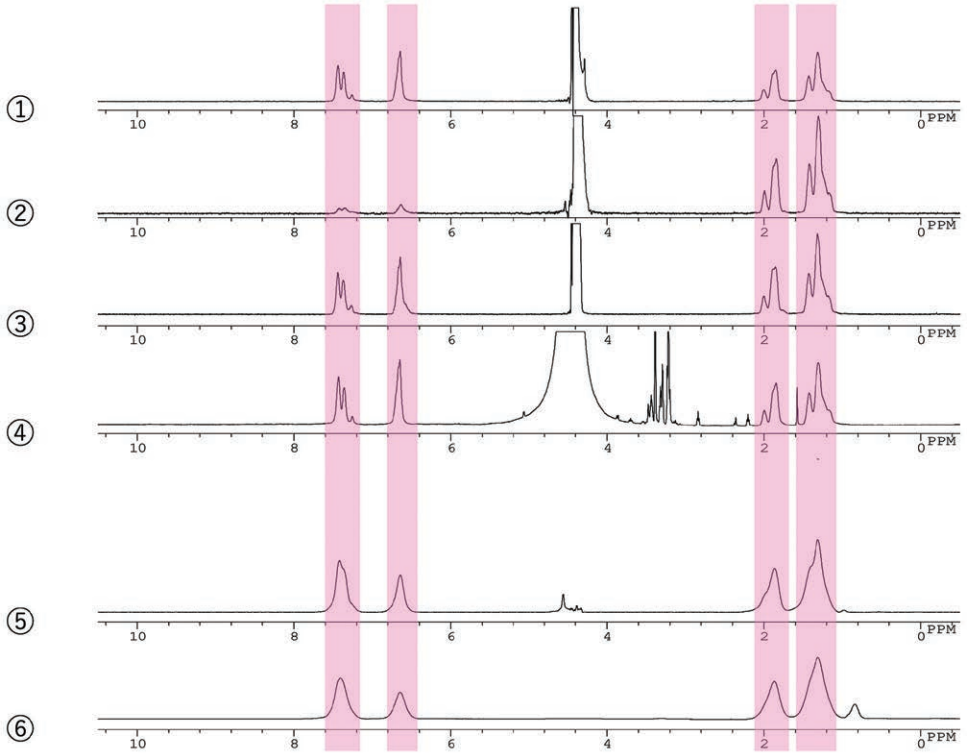

Fig. 1. Proton NMR spectra of the copolyamide and PAAG fillers. The following NMR spectra are shown: ① Los Deline, ② Aqualift, ③ Aquamid, ④ e-PAGEL HR, ⑤ PAAG, and ⑥ Amazingel. The characteristic peaks of PAAG are highlighted in gray. ① to ④ were measured by the FGMAS method, whereas ⑤ and ⑥ were measured by the solution-state method.

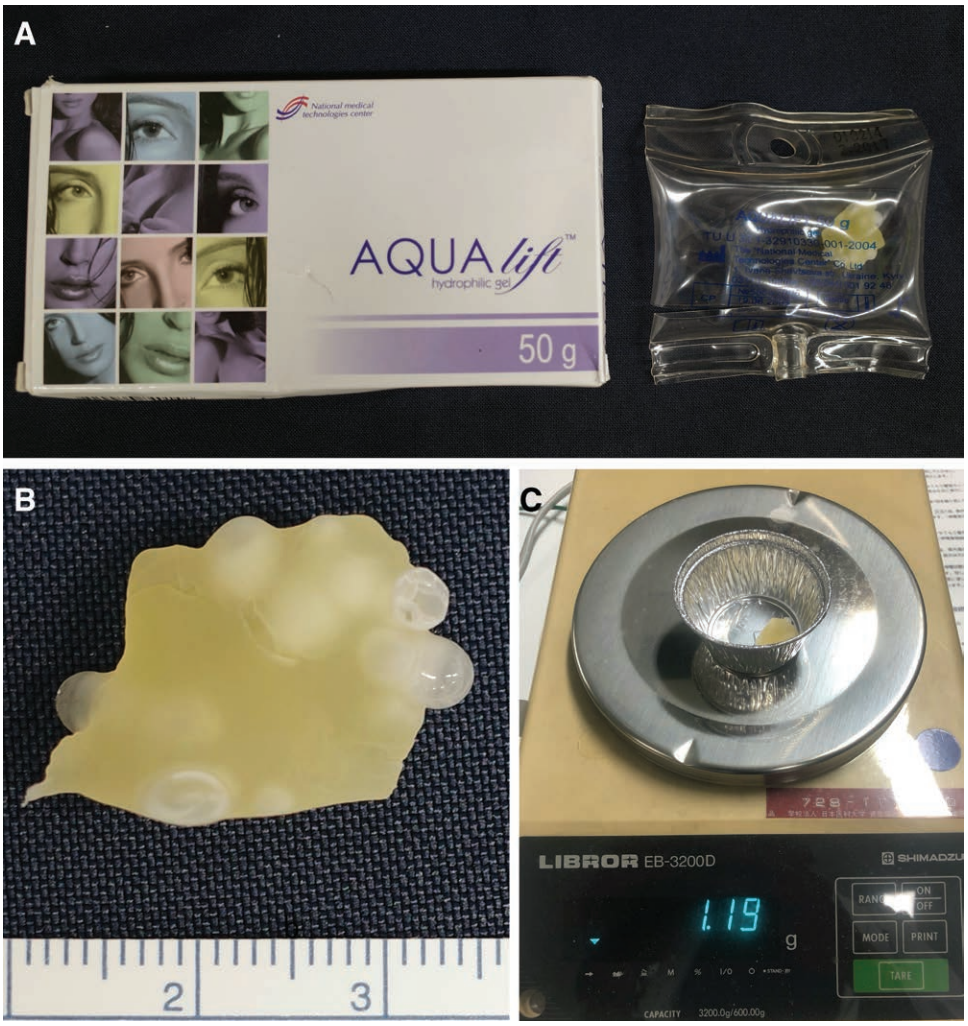

Fig. 2. Appearance of Aqualift when it was left to dessicate for 3 months. A, The product in the open bag. B, The product had become a hard yellow resin. C, The original weight of the product had been 49 g, but it now weighed 1.19 g.

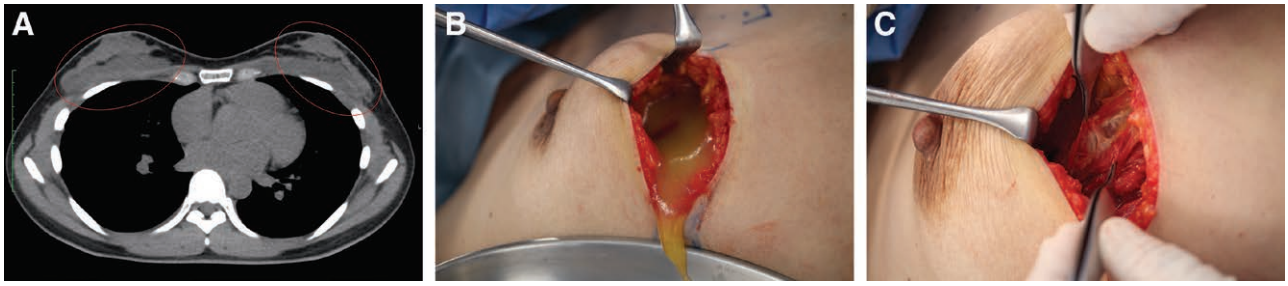

Fig. 3. Case 2. A, The preoperative CT scan showed a low-density area that had spread under both breasts and the pectoralis major muscle. B, A submammary incision opened the submammary storage space. The viscous yellow liquid was drained. C, Intraoperative view showing that the infused Aqualift had infiltrated the pectoralis major fibers and had extended below the pectoralis major muscles.

breasts about 4 years ago. A year later, a small amount of Aqualift was injected into the left breast at another hospital. Immediately after the second injection, the patient noticed that the left breast had become deformed and that the injectate moved under the skin. It eventually reached the vulva and caused a wound. The patient discharged a large amount of gel into the toilet at home via the vulvar wound. At the time she visited our hospital, the left breast had returned to the almost the same size that it was before the first injection (Fig. 4A). A 20-mm fistula was found in the vulva and a small bulge of filler remained under the vulvar skin (arrow in Fig. 4B). Although we are considering a surgical operation to remove the residual filler, the patient has not yet specifically requested this procedure.

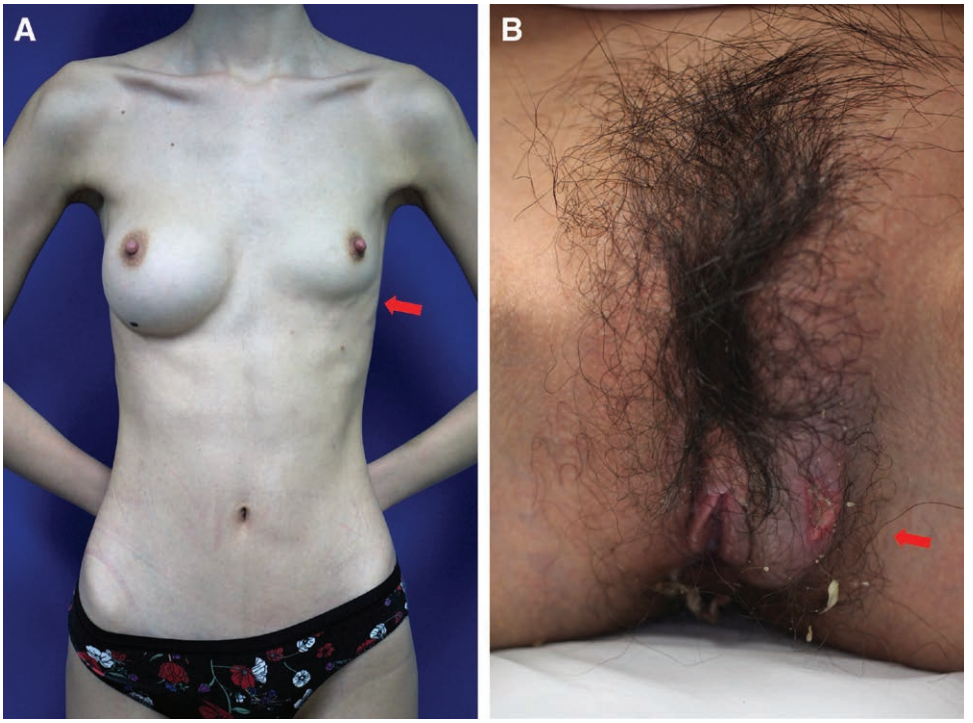

Fig.4. Case 5. A, View of the patient at the time she consulted with us. The formulation that had been injected into the left breast had gradually migrated downward subcutaneously until it reached the pubic area. Nevertheless, the left breast had maintained its shape. B, Once the filler reached the left labia majora, a wound developed and the filler was discharged naturally. The orange arrow shows that some filler was infiltrating the labia majora.

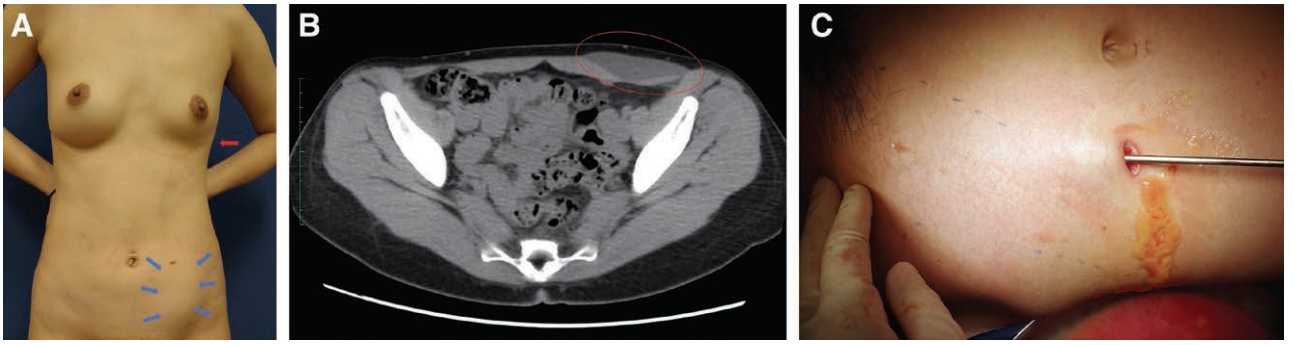

Fig. 5. Case 18. A, The Aquafilling that had been injected into the left breast had moved to the lower left abdomen, where it formed a visible bulge. B, CT showed a low-density area on the rectus fascia at pelvic height. C, Intraoperative findings. Cleaning of the bulge was performed under ultrasonic guidance with a cannula that had been inserted into a pigmented spot caused by insect bites in childhood.

Case 18

This 32-year-old woman underwent injections of 200 g of Aquafilling/Los Deline into both the left and right breasts about 3 years ago. About half a year before her presentation at our hospital, the patient felt a sense of discomfort in the left ribs and her left lower abdomen started to bulge. We observed atrophy of the left breast and an obvious subcutaneous swelling on the left lower abdomen (Fig. 5A). Detailed examination by CT showed a low-density area on the rectus fascia at the site with the visible bulge (Fig. 5B). A large pigmented scar was used for cannulation, and the area was cleaned with jet water flow under ultrasonic guidance (Fig. 5C). The cleaning procedure was successful and removed most of the infusate.

DISCUSSION

PAAG was developed in Ukraine in 1997 and was introduced to the Chinese market under the trade name Interfall.[10] Two years later, a similar product that was developed in China was widely used for breast augmentation under the product name Amazingel. However, multiple reports of complications caused the China Food and Drug Administration to prohibit the use of Amazingel in 2006. It is estimated that in the decade before the ban, 200,000 women in China underwent breast augmentation with PAAG injections.[11] Studies at the time suggested that between 1.44% (12/833) and 18.21% (262/1432) Chinese patients who underwent breast augmentation

with PAAG filler developed complications. Numerous case series studies with sample sizes ranging from 12 to 235 have shown that these PAAG filler–related complications include breast lumps, pain, infection, deformity, inflammation, fistula, and hematoma. For example, Unukovych et al[12] showed that of 45 Ukrainian women who underwent surgery in 1998–2009 to treat PAAG complications, 80%, 74%, 73%, 54%, and 16% had pain, breast hardening, deformity, lumps, and fistulas, respectively. Moreover, the average duration from the injections to developing the complication was 6.1 years.[12]

Given that our patients were a more heterogeneous group and a quarter were asymptomatic, our study was relatively consistent with these findings. Of the 29 patients who received copolymer-filler injections and presented with concerns or complications, 59%, 28%, 17%, 10%, and 3% presented with deformity, gel migration, infection, induration, pain, and fistula, respectively. The mean duration between injection and consultation at our hospital was 1.8 years. These clinical findings indicate that copolyamide filler injections for breast augmentation associate with similar complications as PAAG filler injections.

This is supported by our NMR analysis of the copolyamide fillers, which showed that the composition of both fillers closely resembled that of PAAG, 2 PAAG fillers, and a PAAG electrophoresis gel. Since NMR is used widely by many fields (eg, solid-state physics, chemistry, biology, medical research, and medical diagnosis) to identify the previously unknown composition of a substance, this finding is likely to be highly reliable.[13–15]

Main Complications

Deformity and Infection

The most common complaint in our cohort was deformity, which was observed in 59% of patients. The second most common complaint was infection, which occurred in 28% of the patients. In some of these cases, the infection arose immediately after the injections. Other cases developed mastitis-like symptoms after several years had passed. Both types of infection cases are likely to be due to the injection procedure: the cannula may not have been placed in the correct position and/or its tip may have damaged the submammary fascia. This reflects the fact that it is difficult to inject the filler precisely without skilled procedures that are performed with ultrasound guidance.[16]

Filler Migration

It was once believed that PAAG was migration-resistant[17] because it aggregates strongly and has a large molecular size. The reasoning was that these properties attract fibroblasts and blood vessels, which grow from the surrounding tissues to form capsules around the material. These capsules would theoretically prevent migration and make the filler relatively easy to remove if that was necessary.[18–20] However, in our cohort, we encountered 4 cases (14%) where the preparation had infiltrated into the tissue and/or had migrated out of the breast to distant sites. These cases were particularly difficult to treat (patients no. 2, 5, and 18). Indeed, filler migration is a well-known sequela of Aquafilling/Los Deline.[3,6] This is also true for PAAG fillers, which have been reported repeatedly to migrate.[11,12,21–23] For example, the case series study of Unukovych et al[12] mentioned earlier showed that 14% of their cases exhibited gel migration. Thus, the claim that PAAG materials do not migrate should be rejected. This was also the opinion of the 2016 position statement of the Korean Academic Society of Aesthetic and Reconstructive Breast Surgery.[8]

Our findings in our filler migration cases align with a histological analysis in rats that compared the PAAG filler Aquamid with the hyaluronic acid-based filler Restylane Perlane. That study showed that Aquamid has a higher tissue affinity than Restylane Perlane and, therefore, infiltrates the surrounding tissues and tends not to form capsules, unlike the comparator filler.[24] This is supported by the study of Cheng et al.[23] This tendency together with the proinflammatory properties of PAAG means that when complete encapsulation does not occur, PAAG fillers will induce a prolonged inflammatory response. Our cases of copolyamide filler migration also seemed to be the result of incomplete or unstable encapsulation. The filler in case 5 migrated downward to the vulva, where it was eventually expelled through a vulvar wound. The filler in case 2 also showed migration to under the pectoralis major muscle, where it invaded the muscle fibers. These migrations may reflect gravity and muscle movements.

Notably, cases 2, 5, and 18 also demonstrated retention of the filler in the axilla. In case 2, this may reflect the fact that the cleaning process involved axillary cannulation: this cleaning not only broke the capsule but also created an axillary tunnel through which the filler migrated into the axilla. It should be noted that it was not possible to determine in our cases of filler migration whether the filler had caused swelling of the regional lymph nodes because the lymph nodes could not be directly visualized: either surgery was not performed or the surgery was performed via a small incision.

It should be emphasized here that migration of material after breast augmentation is also not uncommon for other procedures. Two case reports describe the migration of silicone from ruptured silicone implants to the lower limbs.[25,26] Migration has also been observed when fillers are used to augment other body areas, including facial silicone injection,[27,28] brow hyaluronic acid injection,[23,29] and buttock fat injection.[30]

Physical Properties of Copolymer Fillers and Permanence after Injection

In the present study, we observed that when 49 g of Aqualift was inadvertently left exposed to the air at room temperature for 3 months, it solidified into a resin that exhibited some blistering and now weighed 1.19 g. This was 2.43% of the original weight, which is similar to the copolyamide weight/volume of the original preparation, as indicated by the manufacturer (2%). This is visual proof that this formulation has a chemically unstable structure, unlike synthetic polymer compounds such as silicone. Moreover, it seems highly likely that such resin components will persist after being injected into the body.

There is no doubt that copolymer fillers should also be classified as permanent fillers and that they associate with the same clinical risk as PAAG fillers.[11,12,31] However, it should be noted that absorbent (impermanent) fillers such as hyaluronic acid can also cause adverse events when used for breast augmentation. These events include infection and capsular contracture.[32] Moreover, injections of hyaluronic acid through the skin can induce bacterial biofilms (this is also observed for PAAG).[33] The problem with nonabsorbable fillers is that they do not degrade and become absorbed. This persistence has several implications if the filler migrates: (1) the symptoms will be long-term; (2) late complications can occur at any time; (3) the migrated material must be removed, which can be very difficult to achieve when it is broadly dispersed; and (4) migrated material can lead to difficulties during mammography for breast cancer.

Thus, the risks of copolyamide fillers should be seen as being equivalent to the risks of existing PAAG fillers such as Aquamid and Amazingel. These formulations should not be used as breast implants until their long-term safety is well established.

Study Limitations

This study has some limitations. First, there are many PAAG fillers: in 2013, 8 (Aquamid, Interfall, Outline, Formacryl, Bioformacryl, Bio-alcamid, Amazingel, and Argiform) were commercially available.[34] Our NMR study did not test all products. Second, although NMR is an excellent method for determining composition, we recognize that composition is only one property of the fillers. Further testing with additional methods and careful discussion will be required to definitively conclude that the copolyamide and PAAG fillers are identical in all properties. Third, although some of our patients exhibited immunological reactions, we did not test any of our cohort for systemic inflammatory diseases such as autoimmune/inflammatory syndrome induced by adjuvants (ASIA).[35] Thus, it remains to be determined whether copolyamide fillers can induce systemic syndromes such as ASIA.

Despite these limitations, we believe that our findings illuminate the social issues that surround copolyamide fillers. We hope that our study will create a market that both understands the willingness of patients to undergo injection-based breast augmentation and the need to provide safer procedures and materials.

CONCLUSIONS

This study showed that the Aquafilling/Los Deline and Aqualift/Activegel copolyamide fillers appear to closely resemble existing PAAG fillers such as Aquamid and Amazingel in terms of clinical complications and composition. Because there have been many reports of complications after the use of copolyamide fillers and their long-term safety has not been established, these products should be viewed as having the same risks as other PAAG fillers when used for breast augmentation. We strongly recommend not to use these products at the present time.

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