Tissue Integration of Polyacrylamide Hydrogel: An Experimental Study of Periurethral, Perivesical, and Mammary Gland Tissue in the Pig

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BACKGROUND Polyacrylamide hydrogel (PAAG) is a nondegradable water-based polymer with high viscoelasticity. The gel is used as a tissue filler, the only risk being prolonged infection with anaerobic, contaminating microorganisms if not treated early with broad-spectrum antibiotics.

OBJECTIVE With silicone gel as reference, PAAG tissue integration and migration was studied in a longitudinal study of the pig.

MATERIALS AND METHODS Forty-one pigs were used. PAAG and silicone gel were injected into mammary tissue, and PAAG was injected into urethral or bladder wall or the anal canal. Tissues and regional lymph nodes were examined at 1, 1 1/2, 3, 3 1/2, 6, 12, and 14 months, and other lymph nodes and organs were examined at 1, 6, 12, and 14 months.

RESULTS PAAG was invaded by macrophages and giant cells that were gradually replaced by a network of fibrous tissue. Silicone gel was seen inside these cells or as large vacuoles, surrounded by a fibrous capsule. Regional lymph nodes contained PAAG only at 1 1/2 months and silicone gel at 12 months.

CONCLUSION PAAG is a stable, viscoelastic bulking agent, which unlike silicone gel is slowly integrated within its host tissue via a thin fibrous network. Long-term risk of fibrosis and migration is minimal.

This study was financially supported by Contura A/S, Soborg, Denmark.

Injectable bulking agents have been used for more than 100 years in the treatment of wrinkles, scars, defects, reflux, and incontinence,[1–4] but problems with biodegradation, biocompatibility, fibrosis, infection, and migration have prevented their success. Polyacrylamide hydrogel (PAAG) is an atoxic and nonimmunogenic polymer gel consisting of 2.5% to 3.5% cross-linked polyacrylamide and 96.5% to 97.5% water.[5–12] It is resistant to degradation and has a widespread use in ophthalmic surgery, drug treatment, food packaging, and water purification.[5–9,13] PAAG has been used in plastic surgery for aesthetic purposes in the former Soviet Union and China for the past 15 to 20 years,[9–11,14–16] and in Europe for the past 7.[17–21] We have previously shown that the gel stays in human breast tissue for at least 8 1/2 years after the injection and is accompanied by a modest or no tissue reaction without capsular fibrosis or calcification.[10] We have also observed that PAAG injected into the subcutaneous tissue of the human face initially elicits a foreign-body reaction, which disappears with time leaving the host tissue inert to the gel at 3 years.[19] A recently published study in rabbits has shown that the bulking effect is preserved, at least for 7 months.[22] This prospective experimental study on minipigs and normal Danish pigs was undertaken with the sole purpose of testing the histologic effect on host tissue of the hydrophilic PAAG, as opposed to the hydrophobic polymer gel, silicone gel, over time,

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ISSN: 1076-0512 • Dermatol Surg 2008;34:S68–S77 • DOI: 10.1111/j.1524-4725.2008.34246.x

and to study the extent of gel migration, both locally and along the reticuloendothelial system (RES). The gel was injected subcutaneously, submucosally or intramuscularly, and all injected tissue, as well as regional and distant lymph nodes and RES organs, were examined macro and microscopically at 1, 1 1/2, 3, 3 1/2, 6, 12, and 14 months.

Materials and Methods

A total of 41 pigs, 11 normal Danish pigs and 30 Göttingen SPF minipigs, all 3 to 4 months of age, were used. Twelve of the minipigs were injected with low-viscosity (LV) PAAG (Aquamid, Contura A/S, Søbory, Denmark), comprising 2.5% polyacrylamide and 97.5% water, and 12 were injected with a specially produced intermediate-viscosity (IV) PAAG comprising 3.1% polyacrylamide and 96.9% water (R. Smith, personal communication, Chempilots A/S, Farum, Denmark, 2006). Another 6 minipigs were injected with silicone gel obtained from silicone breast prostheses (Allergan, Inc., Irvine, CA; style 20—smooth round silicone). The viscosity of this gel corresponded to that of the HV PAAG.

The normal-size pigs were injected intravesically with the IV and a high-viscosity (HV) PAAG, comprising 3.1% and 3.4% polyacrylamide, respectively (R. Smith, Chempilots A/S) and intraurethrally with the LV PAAG (Aquamid; $n = 6$). An additional five pigs were injected perianally with the IV PAAG ($n = 5$).

All minipigs received six deposits (three on each side) of each 5-mL bolus. Five of the normal Danish pigs received two deposits of each 1 mL perianally, and an additional six received two 1-mL deposits into the bladder wall and two 0.5-mL deposits into their urethral wall. However, because the urethral wall of the pig is very thin—one-third of the size in man—it was noticed that a large part of the gel reached a final positioning along the serosal surface of the urethra—within the pelvic cavity.

The pigs were observed daily for deviations in eating and drinking behavior and physical activity. Blood tests were taken just prior to the injection and during the last week before termination. These include hemoglobin, red cell count, hematocrit, mean cell volume, mean cell hemoglobin concentration, white cell count, differential leukocyte count, platelet count, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin, γ-glutamyltransferase, cholesterol, carbamide, creatinine, glucose, sodium, potassium, calcium, protein, protein electrophoresis, and globulin.

The pigs were euthanized—two or three at a time after 1, 1 1/2, 3 1/2, 4, 6, 12, and 14 months. A macroscopic examination of all injection sites was done by naked eye inspection and palpation (breast deposits) or after dissection (urethra, bladder, and anal canal). Regional lymph nodes were isolated, and after opening the cranial, thoracic, and abdominal cavities, all organs were examined in situ. Microscopic examination using H&E and van Gieson/Alcian blue morphology staining was carried out on all tissues. Pigs euthanized at 1, 3, 4, 6, 12, and 14 months also had lymph nodes examined from the neck, the mediastinum, paraaortically, and the portal area, and pigs euthanized at 6, 12, and 14 months also had random samples, one to five (mean, three), examined from the thymus, lungs, stomach, liver, spleen, kidneys, and nerve system (sciatic nerve or medulla oblongata or brain). Microscopic examination of the bone marrow was made at 6 and 14 months.

The study on minipigs was carried out at the Scantox Laboratories (Lille Skensved, Denmark) in accordance with the OECD principles of good laboratory practice (GLP). The study on normal Danish pigs was carried out at Skejby University Hospital, Denmark, and had been approved by the local ethics committee (No. 1999-1998-561-64).

Results

Clinically, no deviations from normal were observed in regard to behavior, body weights and blood

values, and no treatment-related adverse reactions were recorded. Macroscopically, the PAAG deposits differed significantly from the silicone gel deposits. At 1 month, the large PAAG deposits placed submucosally appeared to have spread out into numerous minor deposits. The same was found at 3, 6, and 12 months with no apparent reduction in bulk size over time. A thin fibrous capsule was noticed in a few of the deposits of HV gel. Silicone gel was seen as one large or a few smaller firm masses of clear material, always surrounded by a 1- to 2-mm-thick fibrous capsule.

Gross inspection of the vesicourethral specimens confirmed that PAAG had been injected into the urethral/bladder wall, both intramurally and into the pelvic cavity, which contained large collections. Submucosal bulges of different sizes corresponding to the gel deposits were seen in all cases (Figure 1). The variation in size occurred at random among the different specimens and from one side to the other of the same specimen. Bleeding was seen in a few cases but there were no signs of hardening or infection.

A total of 254 regional lymph nodes were isolated (52 at 1 and 1 1/2 months; 64 at 3, 3 1/2, and 4 months; 84 at 6 months; and 35 at 12 and 18 at 14 months). They showed variation in size, depending on site and, for regional nodes, time since injection. In PAAG-injected pigs regional lymph nodes were of the same mean size at 1, 1 1/2, 9, 12, and 14 months, but at 3, 3 1/2, 4, and 6 months they were generally enlarged. In silicone gel–injected pigs the regional lymph nodes ($n = 56$) examined at 1 and 12 months were similar to those injected with PAAG at the same times.

All other lymph nodes ($n = 281$ from PAAG injected pigs and 81 from silicone injected pigs) were comparable in consistency and size at all times. All internal organs were normal as well.

On histologic examination, the PAAG looked in all sections like a homogenous mass with numerous empty holes and a tendency to retract itself from boundaries (Figures 1B, 2B–2D, 4, and 5). Silicone

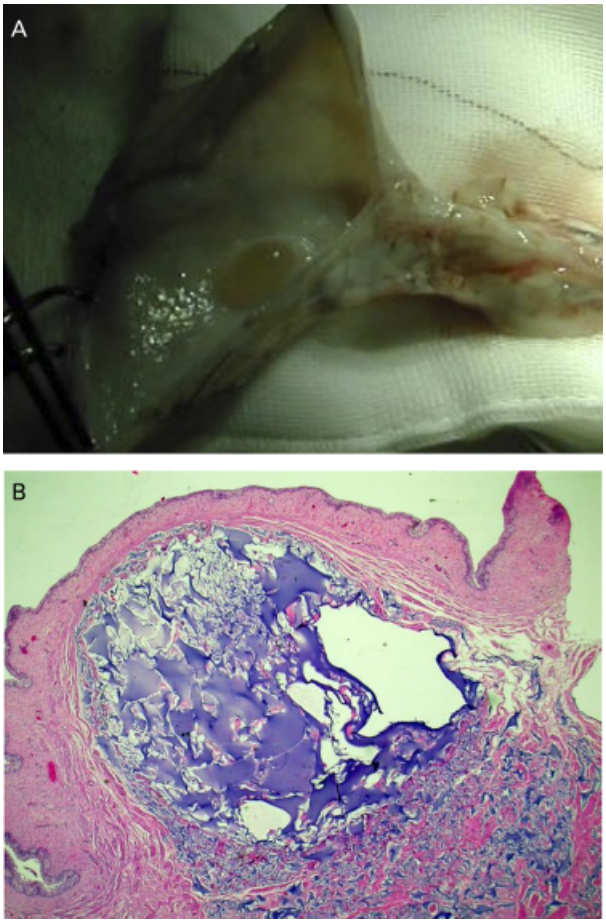

Figure 1. Bladder mucosa containing a large bulge of polyacrylamide gel: (A) macro photo; (B) micro photo (H&E, ×20). The gel is invaded by connective tissue, predominantly toward host tissue not covered by an epithelial lining.

gel appeared in most cases as just a thin, irregular refractile rim along the deposits or vacuoles (Figure 3). The dehydration process, which the tissue section is subjected to during routine processing for histologic examination, was responsible for the PAAG retraction, and the fat extraction process, also part of routine processing, was responsible for the silicone gel loss. Once injected, the PAAG tended to disperse in smaller deposits, lateralizing along natural boundaries (e.g., fascia). This was not seen for the silicone gel. Deposits of the HV PAAG tended to show a more rounded appearance and a slightly darker color than the LV and IV gel types.

Histiocytes (macrophages and foreign-body giant cells) were present in both PAAG and silicone gel

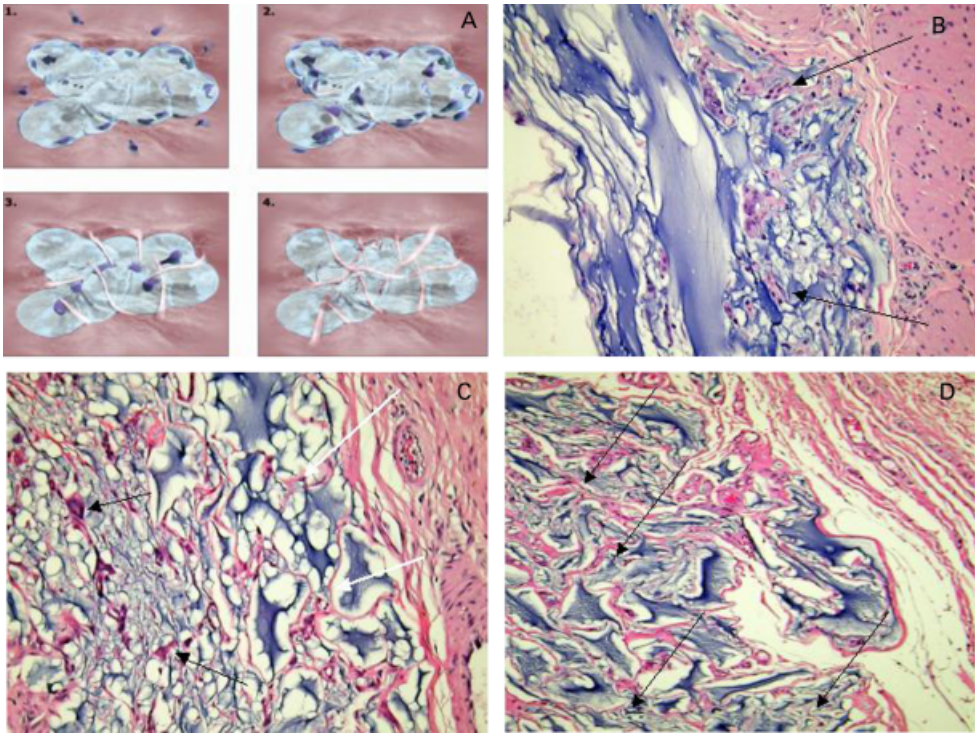

Figure 2. Polyacrylamide hydrogel—host–tissue interaction. (A) A schematic drawing showing the four steps in PAAG tissue integration. Macrophages congregate along the periphery of the gel (1), they start to invade the gel (2), fibrous strands are emerging (3), and a complete fibrous network has formed (4). (B–D) Histology of PAAG–tissue interaction (H&E, × 40). In the beginning most macrophages and giant cells appear at the outer rim of the gel deposit, adjacent to the host tissue (B, arrows). Later, most macrophages and giant cells form a network within the deeper part of the gel deposit (C, black arrows), whereas the outer rim is traversed by a network of connective tissue fibers (C, white arrows). At 14 months, most of the gel deposit is traversed by a network of connective tissue fibers (D, arrows).

deposits. However, whereas these cells had engulfed the silicone gel (Figures 3C and 3D) or surrounded the gel (Figure 3), they had entered the PAAG and were gradually replaced by a fibrous network, the progress of which depended on the size of the gel deposit and its relation to a covering surface (Figures 1B and 2).

With the exception of one area with a small calcification within the bladder epithelium, the covering surface (skin, mucosa) was intact and normal looking. Neither PAAG nor silicone gel deposits showed any signs of fragmentation, calcification, necrosis, or infection.

Passive Migration

At sites where large PAAG collections had been observed lying freely in the pelvic cavity, the adjacent fat showed a more pronounced host reaction (Figure 4). A 50-μm broad rim, consisting of an irregular mixture of macrophages, foreign-body giant cells, and gel was seen at 1 1/2 months (Figures 4A and 4B). A similar but only 30-μm rim was seen at 3 1/2 months (Figure 4C), and at 14 months only a thin rim, consisting of mainly connective tissue, remained (Figure 4D).

Regional lymph nodes and a few neck lymph nodes showed evidence of forced migration (high injection pressure) or passive drainage from large PAAG masses injected erroneously into the pelvic cavity. Sixty percent of local lymph nodes from the breast region and 40% of local lymph nodes and one section from the spleen capsule from the perivesical region showed gel within their lymph vessels. This was seen for PAAG (Figure 5) as well as for silicone gel (Figure 6). Local lymph nodes and vessels from the anal region with only small intramural deposits contained no gel.

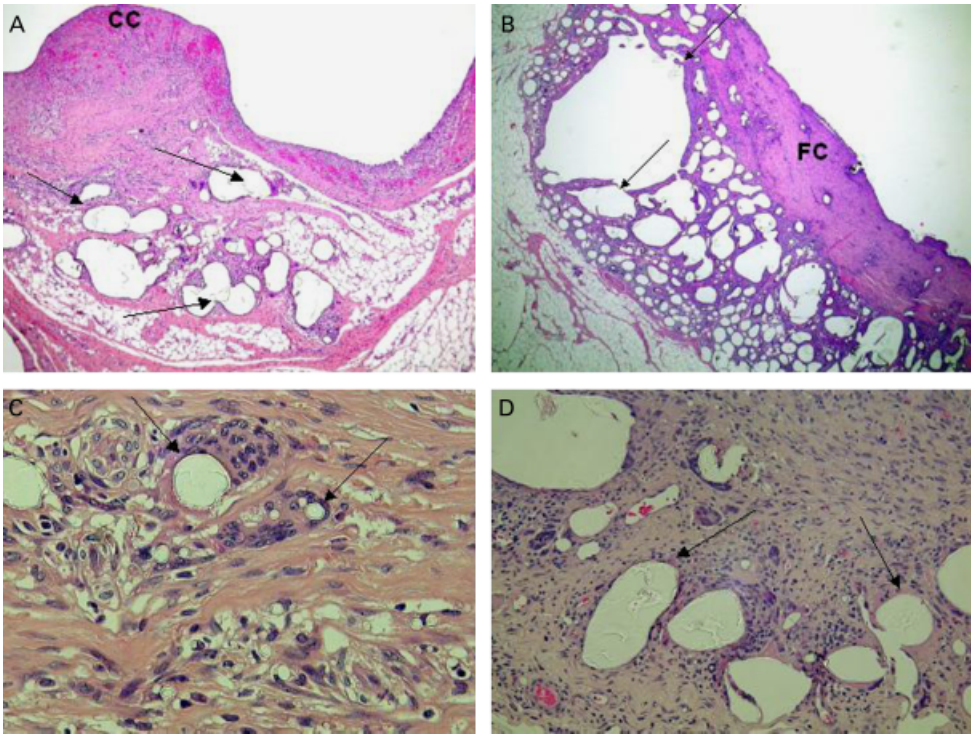

Figure 3. (A) Silicone gel deposit at 1 month consisting of vacuoles (arrows) surrounded by histiocytes and a cellular capsule (CC). (B) At 12 months the capsule is more fibrous (FC). At both 1 and 12 months, macrophages and giant cells contain large droplets of silicone (C, arrows), which are coalesced into larger vacuoles (D, arrows), surrounded by these cells (C, H&E, × 40) and (D, H&E, × 60).

Active Migration

Evidence of a transient macrophage-mediated regional migration of PAAG was seen at 1, 1 1/2, 3, and 3 1/2 months with recognizable PAAG at 1 and 1 1/2 months (Figures 7 and 8). The number of cells and the overall lymph nodes size was reduced at 12 and 14 months.

Evidence of a macrophage-mediated migration was also seen for the silicone gel, but only at 12 months. Small silicone droplets appeared within sheets of macrophages, located within the lymph node sinuses (Figure 9). All other lymph nodes looked normal.

Discussion

This experimental study was undertaken with the sole purpose of systematically investigating the histologic and biologic effect of PAAG on soft and muscle tissue. Clinical studies have shown that PAAG is an excellent filler for soft tissue augmentation,[10,11,17,18] just as silicone gel has been used successfully in intradermal applications, e.g., acne scarring.[23] However, we did not have a direct translation of the results into a clinical setting in view but were only interested in how the hydrophilic PAAG as opposed to the hydrophobic silicone gel would interact with surrounding host tissue.

We chose the pig, because it is the experimental animal closest related to man in respect to anatomy and histology, and a reason for using large gel deposits was the higher probability of obtaining and hence detecting regional or distant migration. In accordance with a recent experimental study in rabbits[22] and several clinical studies,[17,18,20,21] we could confirm that PAAG retains its bulking effect for a long time. Optimally, the study should have been carried out for up to 5 or 10 years to test permanency and long-term effects of both gels, but a maximum follow-up of 14 months gave sufficient insight into the

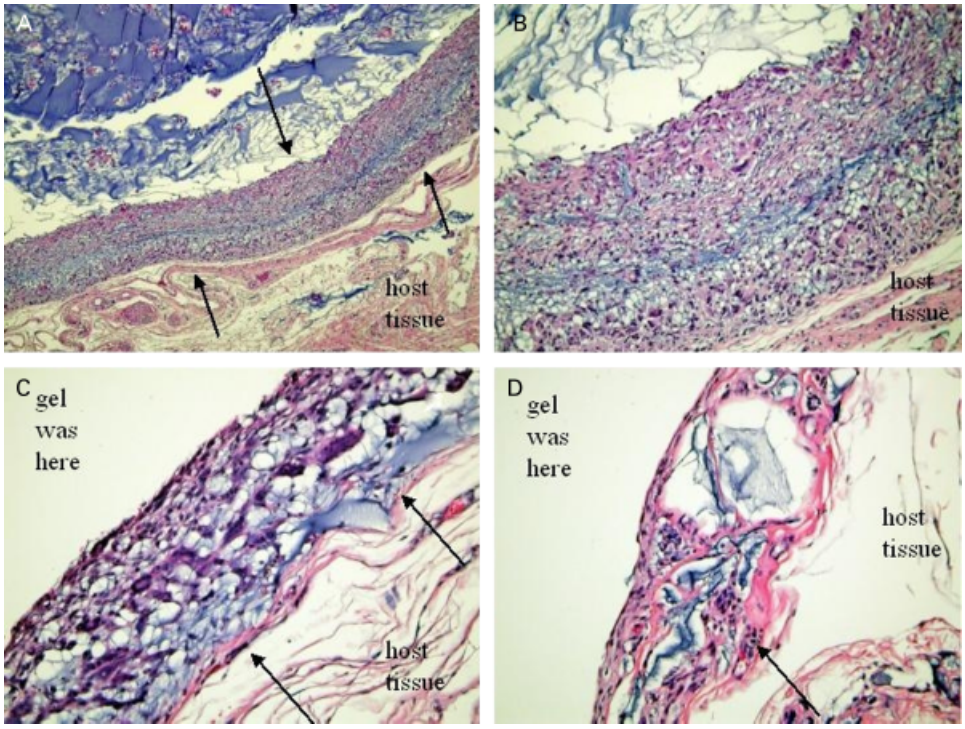

Figure 4. Host reaction to large gel deposits. (A) At 1 1/2 months, a thick rim consisting of macrophages, foreign-body giant cells, and gel has formed around large gel deposits lying in the loose host connective tissue (arrows; H&E, × 20). (B) Close-up view of the cellular rim seen in (A), displaying individual cells (H&E, × 40). (C) At 3 1/2 months, a thinner rim appears around the large gel deposits (arrows). Gel, which has been present centrally in the deposit (top left), has been extracted during histological processing (H&E, × 60). (D) At 14 months, the rim consists mainly of connective tissue and gel. Only a few macrophages and giant cells remain (arrow; H&E, × 40).

integration process for the peripheral borders of the PAAG deposits, and it must be assumed that the integration process continues, as long as untraversed gel remains.

The control gel (silicone gel) also retained expectedly its bulking effect, but as a hydrophobic gel, it was not, like PAAG, entered by macrophages and giant cells. Instead it was seen inside these cells or it

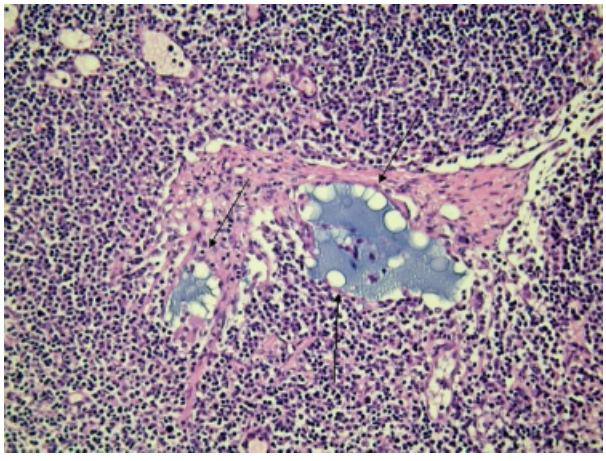

Figure 5. Connective tissue trabeculum of a regional lymph node containing PAAG within a small lymph vessel (arrows; H&E, × 40).

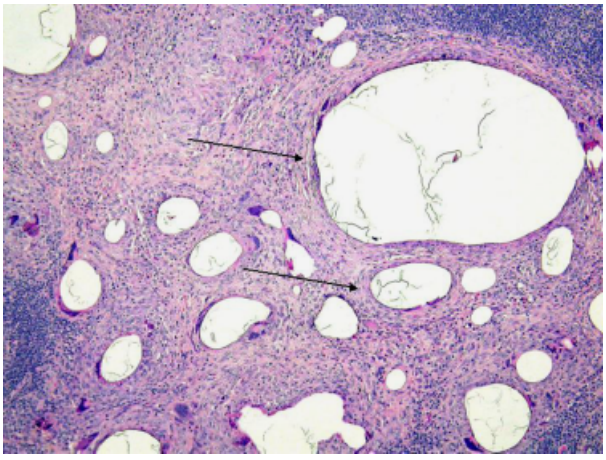

Figure 6. Connective tissue trabeculum of a regional lymph node containing vacuoles of silicone gel (arrows; H&E, × 40).

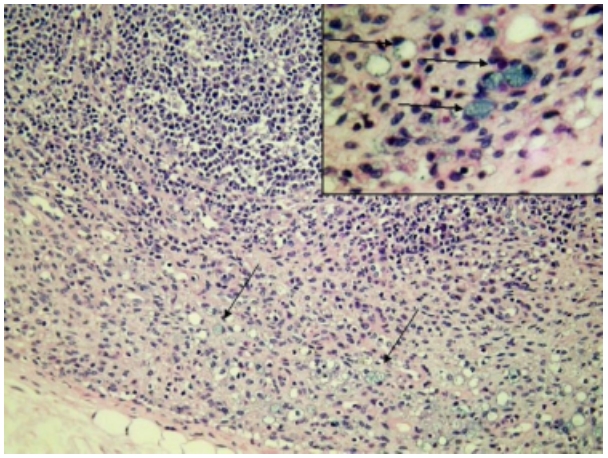

Figure 7. Regional lymph node with a subcapsular collection of macrophages containing PAAG (arrows; H&E, ×40). Inset: close-up of the macrophages (arrows; H&E, ×90).

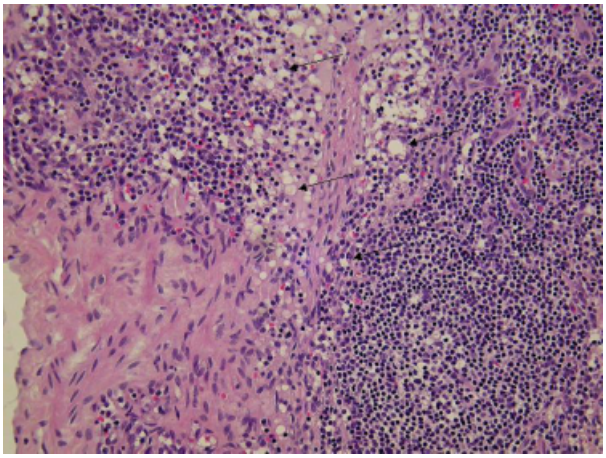

Figure 9. Regional lymph node with macrophages containing a slightly refractile material within their cytoplasm (silicone gel; arrows; H&E, ×60).

formed vacuoles surrounded by a firm capsule of fibrous tissue.

Prospective clinical studies of patients being treated with PAAG for aesthetic purposes,[17,18] human immunodeficiency virus lipoatrophy,[20] and stress urinary incontinence[21] have already been published, and more are under way. Clinically, the gel appears to be effective and long-lasting, with no tissue hardening or local dissection/migration—complications that have been described for some of the other fillers.[24–26] The advantage of PAAG is its viscoelasticity and high water content, which gives it a constant molecular interaction with its surroundings. This probably facilitates the in situ anchoring by the fibrous network seen in this study and prevents, in contrast to silicone gel, the formation of a thick fibrous capsule, which gives tissue hardening and calcifications. The only disadvantage of the gel is the infection risk.[19,27] The incidence of infection following injection is the same as for other fillers (approximately 0.1%), but the atoxic PAAG serves as an excellent growth medium for bacteria, and if not treated immediately with broad-spectrum antibiotics in high dosage, the infection can be long-lasting and difficult to treat.[27] On the other hand, the infection risk is always associated with the injection procedure, and late debut of an infection (more than 1 year after the injection) has not been described.[27] Once the gel has been integrated within the tissue and a network has formed with scavenger cells close at hand, a de novo infection is unlikely to develop.

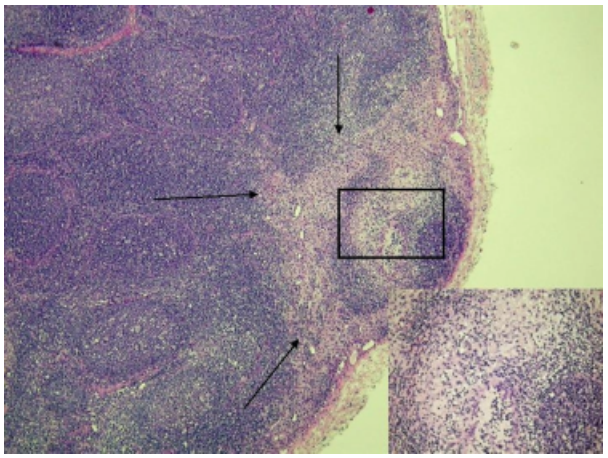

Figure 8. Regional lymph node containing an area of subcapsular histiocytosis (arrows; H&E, ×25). Inset: a close-up of the area (H&E, ×40).

PAAG consists of 97.5% loosely bound water molecules, which are easily exchanged with the surroundings, i.e., the extracellular matrix. Two different type observations support this. In one, methylene blue was added to the gel, which after having been injected subcutaneously in the abdomen of minipigs, disappeared within 1 day (own unpublished observations). The other showed that

radioactively labeled water molecules in PAAG were quickly exchanged with surrounding water (J. Brahm, personal communication, 2007). Such a dynamic exchange of water molecules would provide the gel with a constant undulating motion on a microlevel, preventing not just capsule formation but also diffuse fibrosis—a problem that has been described for some of the more static bulking agents such as the polypropylene mesh used in urine incontinence[28] and the combination gels (suspensions consisting of solid particles and a transient carrier gel).[19,24]

The observation that PAAG, unlike silicone gel, is integrated into the host tissue by ingrowth of a vessel-bearing fibrous network is new, but vessel ingrowth into the PAAG has been described before in a rabbit study.[29] Furthermore, studies on human facial soft tissue augmented with 1- to 2-cm^3 deposits of PAAG have shown that these have obtained full integration with a mature network at 2 and 3 years.[19] In contrast, large deposits of 200 to 300 cm^3, e.g., for breast augmentation or body sculpturing purposes, still retain some free gel after 8 1/2 years,[10] and serious complications, which needed surgical and antibiotic treatment, have been described several years after the injection.[14–16] An explanation of this phenomenon may be that PAAG deposits of this size, if not contaminated during the injection, may have been contaminated at a later time, giving rise to a low-grade infection. The network buildup starts peripherally, and the smaller the deposit the faster and more effective the tissue integration with ensuing antibacterial effect from circulating blood leukocytes.

In contrast to silicone gel, which was seen within most histiocytic cells of the gel deposits, PAAG of the types used in this study was not normally observed within these cells. However, we saw small collections of gel-laden macrophages beneath the capsule of regional lymph nodes during the early stages of gel/tissue integration, which must have originated from the injection site. These macrophages were only seen at 1 and 1 1/2 months and not at any later time, suggesting the early transient clearance of a minute inevitable fraction of less firmly bound polymer (R. Smith, Chempilots, personal communication, 2007). In accordance with this we saw enlarged lymph nodes with a thick subcapsular rim of macrophages without gel remaining at 3, 3 1/2, 4, and 6 months and normal-size lymph nodes and no subcapsular histiocytosis at 12 and 14 months.

A more prominent migration to regional lymph nodes has been described for silicone gel, especially in women with silicone breast implants.[30] This product was described histologically as partially empty "droplets" of a slightly refractile, peripherally located material within the tissue or lying within macrophages and foreign-body giant cells, just as we found in this study. It seems as if the silicone gel migration by macrophages occurs at a slower pace than the transient PAAG migration. We found just a few scattered sheets of macrophages distended by silicone (Figure 9) appearing no earlier than 12 months. However, others have described a more significant spread to regional lymph nodes years after tissue injection or silicone gel implant insertion, although further spread to the RES was considered negligible.[31]

Conclusion

By injecting PAAG and silicone gel into breast subcutaneous tissue, the urethral, the bladder, or the anal wall of 41 pigs, and euthanizing them at 1, 1 1/2, 3, 3 1/2, 6, 12, and 14 months, the gel–host interaction was examined, not just locally on muscle and connective tissue but also on regional lymph nodes and organs of the RES. In contrast to silicone gel, which was surrounded by a thick fibrous capsule, PAAG was anchored to host tissue by thin strands of a fibrous network. First, macrophages and giant cells entered the gel and then thin fibers of connective tissue emerged, and finally, a delicate network of mature connective tissue formed and the cells disappeared. A transient, early migration of a minute amount of gel, probably representing a less firmly bound fraction of the polymer,

occurred for PAAG, whereas incipient silicone gel migration was seen at a later time.

Acknowledgments The authors thank Richard Schmidt, MSc, and Robert Lessel, MSc (Chempilots A/S, Farum, Denmark), for skillful advice during the preparation of the study and for valuable comments on the results.

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COMMENTARY

As we are exposed to more of the permanent fillers from Europe, it becomes increasingly important to understand the histology of tissue integration and its ramifications of potential infection and foreign-body granulomatous reactions. This elegant basic pathology study is a help in our understanding of the pros and cons of long-lasting fillers.

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