

### **Literature Discussion**

Beraka (1995) cited three case reports, in which "the sequence of events was very suggestive of implant rupture during mammography. There was a unilateral rupture in two of the patients and bilateral rupture in the third. All these patients had subglandular silicone gel implants. In each of the affected breasts, there was sudden severe pain on compression during mammography, and this pain lasted several days. These patients had class II or III capsular contracture. One patient underwent augmentation 20 years ago and the other two within the last 5 years. In one patient the pain on breast compression radiated toward the twelve o'clock position, which was where the free silicone tracking in the breast tissue was seen on the mammogram."

000046

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Pickford and Webster (1994) discussed a single case report, in which the patient experienced vague discomfort within her right breast approximately two weeks after a routine screening mammography. During the routine screening of this patient, additional films had to be taken since the initial films were considered inadequate. The patient recalled "significant compression being applied to the breasts to obtain satisfactory radiographs on the second occasion, but experienced no immediate discomfort." Pickford and Webster indicated that the clinical suspicion of rupture was subsequently confirmed during surgery when the right prosthesis was found to have been ruptured. They attributed the implant rupture to be due to the compressive forces applied during mammography.

Williams (1991) described a single case report of a woman who "presented with pain and swelling over the lateral chest wall and adjacent axillary region following a mammogram a few weeks before." The patient observed that "during this procedure, when more compression than usual had been applied, she noted a 'popping' sensation at the time of the exposure." Approximately three weeks later an additional mammogram was performed. "It was noted that a number of irregular globules now appeared on the film where the previous mammogram showed implant distortion." The right implant was found, upon surgical investigation, to be "extensively ruptured, with silicon[e] lying free in the cavity and the bag collapsed within the silicon[e] gel."

Eklund (1990) described a case of 'capsulotomy' (as opposed to rupture) occurring during mammography. During the mammographic procedure, "an audible pop was heard when the compression paddle was applied in the oblique position." The breast that had been firm and erect, was "suddenly soft; it had a normal contour, but also normal droop". The breast was imaged a second time and no change was observed with respect to the first film. Eklund recognized that, since capsulotomy can occur then, "the possibility of damage to an implant by compression during mammography certainly exists, although the event must be extremely rare." However, Eklund cautioned, "Although I applaud the reporting of this event, it should not deter continued appropriate mammographic imaging of the augmented breast."

De Camara *et al.* (1993) provided the findings of a retrospective study of silicone gel breast implants in 31 women. Three patients "described severe burning pain in the breast, radiating to the axilla during mammography. Change in the contour of the breast also was noted. All three of these patients had removal of ruptured older implants ranging from 8 to 14 years." De Camara indicated that "mammograms are usually not considered traumatic and are commonly performed in the augmented and reconstructed breast." However, in light of his findings, he recommended that "mammography may need to be performed more carefully with the older silicone implant."

Although these reports consist primarily of "anecdotal" case studies, in which it is difficult to draw conclusions as to the "significance" of this event, the literature suggests that mammography can produce sufficient compressive forces to result in implant rupture. Furthermore, the literature also demonstrates that routine mammographic screening has been identified as possibly contributing to gel-filled breast implant rupture or as a potential source of damage to the implants.

000047

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000048

In the literature review previously submitted in Module 5, the topics of gel bleed and rupture were discussed on page 28 of Attachment 18 in Volume 9. The citation for the information referenced in the question above was inadvertently omitted from the text. However, the citation was provided in Table 7 of Attachment 18, on page 38 (Robinson et al. 1995), with the complete reference provided on page 115. That reference is as follows: Robinson, C.G., Bradley, E.L., and Wilson, D.S. 1995. *Analysis of explanted silicone implants: a report of 300 patients*. *Ann. Plast. Surg.* 34:1-7. A copy of this reference, as well as any references cited below, are provided in Attachment 14.

As indicated above, the topics of gel bleed and rupture were addressed in the literature discussion (Module 5, Attachment 18), provided on page 28. As part of that discussion, literature concerning silicone migration and extravasation and the resulting potential outcomes of lymphadenopathy and silicone granulomas were also identified and cited. However, Inamed is providing the following literature discussion to expand on the issue of the consequences of gel migration.

Silicone migration can result from either the passage of minute amounts of the gel through the intact silicone elastomer envelope ("gel bleed") or from the release of gel due to rupture of the envelope. Closed capsulotomy, which has been linked by some investigators to implant rupture and/or leakage, subsequently could result in release of extracapsular silicone. Therefore, this procedure is strongly discouraged in Inamed's product literature.

A local site of migration for silicone gel released from breast prostheses has been the breast parenchyma (Argenta, 1983) or lactiferous ductal system. Gel expressing from the nipples has been described by Holten and Barnett (1995) and commented upon by Bloomenstein (1995). Implant rupture accompanied by breaches in the capsule can allow extracapsular gel to infiltrate the breast tissue. Depending on the clinical findings, removal of the extruded gel may include the sacrifice of breast parenchyma.

One of the most commonly reported migration sites for silicone gel released from breast prostheses has been the regional (i.e. axillary) lymph nodes. As a consequence of gel migration to the lymph nodes, silicone associated lymphadenopathy (considered

000049

CONFIDENTIAL

generally to be any disease that affects a lymph node or nodes) and/or lymphedema (swelling as a result of an obstruction of lymphatic vessels or nodes that causes a build up of lymph in the affected region) may develop. Hausner et al. (1978 and 1981) described case reports in which a foreign body reaction to silicone gel was evident in the axillary lymph nodes eight to ten years after implantation surgery. As discussed by Brown and coworkers (1997) "Many case reports and series have described migration to the axillary nodes. Silicone lymphadenopathy in the absence of apparent rupture has also been reported". Lymphadenopathy and lymphedema were previously discussed in the literature review in Module 5 on page 36 of Attachment 18.

Additionally, the bulk movement of gel released from the breast implant to distant locations in the body has been described in the literature. "Silicone gel can also migrate from breast implants through soft tissues to a variety of sites including the antecubital fossa, the upper arm, the chest and shoulder, and along the chest and abdominal walls as far as the groin" (Travis et al. 1985). This review article by Travis and his coauthors also noted that rupture was evident in each of the cases in which distant migration of silicone occurred. This observation of distant migration of silicone gel following rupture of gel-filled prostheses has been described historically by a number of authors (Ahn and Shaw 1994, Capozzi et al. 1978, Foster et al. 1983, Goin 1978, Hirmand et al. 1994, Huang et al. 1978, Mason and Apisarnthanarax 1981, Persellin et al. 1992, Teuber et al. 1995).

Other consequences of silicone migration may include "silicone granulomas," "silicone nodules" and "siliconomas", which have been discussed in the literature (Anderson et al. 1996, Meyer et al. 1998, Teuber et al. 1999). These terms all describe soft masses of encapsulated silicone material found in tissue, and refer to a normal response of the body to foreign material; they do not represent a preneoplastic growth, nor are they associated with any type of carcinogenesis. As stated by Austad (2002), "it is particularly important to note that the formation of a granuloma is not a disease process but rather a type of foreign body reaction. The 1998 report of the Independent Review Group to the British government states this quite succinctly: 'The overall biological response to silicone is consistent with conventional forms of response to foreign materials, rather than an unusual toxic reaction.'" Previously, silicone granulomas were addressed and a frequency rate was provided in the Module 5 literature review on page 36 of Attachment 18.

Regarding the clinical significance of the outcome of gel migration (i.e., silicone granulomas and silicone lymphadenopathy), a review by Travis and coauthors (1985) generally concluded that "critical reassessment of the silicone-related complications reported to date seems to support the continued use of most of the currently available silicone-containing medical prostheses and equipment". A comment was also included by Nalbandian et al. (1983) that "the low incidence and relatively minor consequences of foreign body reactions in the synovium or regional lymph nodes do not constitute a contraindication to the use of silicone as a prosthetic implant material."

Few authors have provided frequency rates for gel migration. Two recent references, Brown et al. (2002) and Robinson et al. (1995), were previously provided in the Module 5 literature discussion and their findings are reiterated below; Nelson (1980) is provided

000050

CONFIDENTIAL

for historical perspective. Brown et al. (2002) reported that out of 344 women in their study, 73 women (9.6%) had extracapsular silicone detected. Robinson et al. (1995) reported 20% (60/300) of patients experienced gel bleed or migration. Nelson (1980) reported on the results of a physician survey of 756 physicians. Of the 756 physicians participating in the survey, five cases of distant migration were reported out of the estimated 114,617 silicone gel-filled breast implant augmentation procedures performed. This represents an incidence rate of approximately 0.004%.

In addition to the review of the literature provided above, information pertinent to silicone gel bleed and migration is available from the Inamed complaint system. Migration of silicone gel from silicone-filled breast prostheses has been the subject of several gel-filled breast implant Inamed complaints and MDR filings. A total of 37 MDRs for gel migration for the devices that are the subject of this PMA have been reported to FDA over the past ten years. An analysis of the Inamed complaint database indicates a 0.02% incidence rate of complaints for gel migration.

Furthermore, information pertinent to silicone gel bleed and migration is available from a review of the Inamed Core Clinical Study data. Physician evaluations of explanted devices were collected regarding the presence of *Gel on Implant Surface* and *Extracapsular Gel* in Inamed's Core Clinical Study of McGhan Silicone-Filled Breast Implants. Of the 31 explanted patients (58 implants) in the Augmentation Cohort, physicians observed 2 ruptured implants with surface gel, while no gel was observed either on the implant surface or extracapsular for the other 56 intact devices. Of the 46 explanted patients (56 implants) in the Reconstruction Cohort, physicians observed 6 ruptured implants with surface gel; no gel was observed either on the implant surface or extracapsular for the other 50 intact devices. Of the 27 explanted patients (46 implants) in the Revision Cohort, physicians observed 2 ruptured implants with surface gel, while no gel was observed either on the implant surface or extracapsular for the other 44 intact devices. Please refer to Table 175 in each cohort for physician evaluations of explanted devices in the Core Clinical Study (Attachment 2 for Core Augmentation, Attachment 3 for Core Reconstruction and Attachment 4 for Core Revision).

While a review of the literature, Inamed complaint database and Core Clinical Study data all indicate that the migration/bleed of silicone gel from silicone-filled breast implants can occur, it should also be noted that silicone-filled breast prostheses are not the only source of polydimethylsiloxanes to which individuals are exposed. The widely used antifatulent, simethicone, is composed of polydimethylsiloxanes. Silicones are used in a variety of medical devices, including use as internal lubricants in disposable syringes. The lifelong repeated exposure to silicone associated with these other medical uses provides a useful perspective on human exposure to silicones from silicone-filled breast prostheses. There has been no evidence to indicate the accumulation of silicone from regular exposure to these other medical devices is harmful to patients.

Furthermore, the National Science Panel appointed by the Honorable Sam C. Pointer Jr. "reaffirmed the low systemic toxicity of silicone." The report reiterated that "results of this review indicate that the silicones used in SBIs [silicone breast implants] are of very

000051

CONFIDENTIAL

low toxicity to animals. Although there is documented evidence of local inflammatory reactions to silicone breast implant materials in animals, there is no convincing evidence for a significant systemic inflammatory response. The local reaction to silicone is similar to other 'foreign body reactions' described with other implanted materials." In its conclusion, the National Science Panel confirmed that "the preponderance of evidence from animal studies indicates little probability that silicone exposure induces or exacerbates systemic disease in humans." (Diamond et al. 1998)

In summary, as stated by the Independent Review Group (IRG) (1998), "the effects of a rupture may be local and/or regional. There are reports of silicone gel having migrated to distant parts of the body such as the arm or trunk, but these are rare." Moreover, the IRG indicated that "in the vast majority of extracapsular ruptures the gel is still in the region of the original pocket and can be removed when the ruptured implant is removed." Although silicone lymphadenopathy and granulomas do occur, their clinical significance is questionable. As stated by IRG, "The substantial risk of implants, as shown in experiments in animals and in other laboratory studies, and as borne out by the much more limited investigation of samples from women with implants, are local inflammatory and scarring reactions, and local infection, as around any foreign body in the tissues." The IRG concluded that "there has been no clinical, laboratory or pathological indication of unusual or unique types of reaction."

000052

CONFIDENTIAL

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000053

CONFIDENTIAL

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000054