The Ongoing Debate regarding Long-Term Safety of Silicone Breast Augmentation Rages

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KEY WORDS: silicone, breast augmentation, safety, autoimmune reaction

IMAJ 2016; 18: 754–755

In this issue of *IMAJ*, Klang et al. [1] report the results of their study on the association between lymph node enlargement and silicone breast rupture. Breast augmentation has become the most popular cosmetic surgery procedure in the world. According to the American Society of Plastic Surgeons 2015 report, 279,143 patients underwent a breast augmentation procedure in the USA in 2015. Of these, silicone implants were used in 80% and saline implants in 20% [2].

The first breast implant surgery was performed in 1895 at the University of Heidelberg in Germany. It was a reconstructive surgery after removal of a large benign tumor and included fat tissue implant from the patient's hip. Since then, various implant materials, including paraffin, glass balls, beeswax, silk fabric, Teflon and even cobra venom have been used. Most of them resulted in severe local and systemic complications.

Silicone gel-filled breast implants were introduced in the United States in 1962. In the 1976 Medical Device Amendment of the Food and Drug Administration (FDA), breast implants were considered to be devices of moderate risk [3]. In 1992, due to reports on frequent local complications, adverse outcomes, and case reports describing cancer and connective tissue disease in some women with breast implants, the FDA removed all silicone gel-filled breast implants from the market. The FDA required manufacturers to submit premarket approval applications that contained data on safety and effectiveness for any new devices. Over the next 14 years, due to the unavailability of silicone gel-filled implants, many women opted for saline-filled implants.

In November 2006, based on clinical trial data from the manufacturers of silicone gel-filled breast implants, which demonstrated its safety, the FDA re-approved silicone gel-filled breast implants for breast reconstruction for women of any age and breast augmentation for women at least 22 years old [3]. Each manufacturer was required to conduct six post-approval studies to demonstrate the safety of the devices. These studies concluded that the risk of complications or adverse outcomes – such as capsular contracture, reoperation, implant removal, implant rupture, wrinkling, asymmetry, scarring, pain or infection – increases with time. Evidence regarding the incidence of connective tissue disease and cancer in those studies was limited [3].

Balk and colleagues [4] recently published a large, systematic review of 32 studies on the long-term health outcomes of silicone breast implants. Although the review was comprehensive, they did not find a significant association for most outcomes. They showed a possible association with increased risk for lung cancer and for some connective tissue disorders such as rheumatoid arthritis, Sjogren syndrome and Raynaud syndrome. Evidence on breast implants and other outcomes was either limited or non-existent. They concluded that better evidence from larger studies is needed to clarify the associations between silicone gel implants and different health outcomes [4].

INFLAMMATORY CONNECTIVE TISSUE DISEASE

In the rheumatology clinic we occasionally see women who developed inflammatory connective tissue disease after silicone implantation (described by us previously) [5]. Case reports and small studies describing an increased incidence of inflammatory connective tissue disease in patients who underwent silicone gel-filled breast implantation have been published in the medical literature. Silicone was also associated with Autoimmune/inflammatory Syndrome Induced by Adjuvants (ASIA) as a possible adjuvant [6-9]. Most of the reports concerned fibromyalgia, scleroderma and systemic lupus erythematosus.

As mentioned above, the post-approval studies of the manufacturers of silicone gel-filled breast implants (10 years of follow-up) as well as Balk's meta-analysis [4] and other reviews and meta-analyses [10-14] were not able to determine a clear, direct association between connective tissue diseases as a group and silicone gel-filled breast implants. This might be explained by the problematic methodology of the studies. They were not large enough or long enough and had inadequate adjustment for likely confounders to demonstrate an association. Holmich et al. [15] hypothesized that implant rupture could prompt an immunological reaction giving rise to autoimmune diseases, but they were not able to prove this theory.

In their article in this *IMAJ* issue, Klang and colleagues [1] provide an interesting and original view. They demonstrate a clear association between implant rupture and axillary lymphadenopathy, which represents a local inflammatory response. Many questions arise from this association. Is there an association between the local

complication (lymphadenopathy) and possible future systemic complications? Could intra/extracapsular rupture affect the development of systemic inflammatory/autoimmune diseases? Could the axillary lymphadenopathy be a predictive sign of a possible, future, systemic inflammatory reaction? Should these women undergo special follow-up? Should we inform our patients about these possible complications? To answer these questions, large prospective studies with long-term follow-up of women with implant rupture are required. If such a connection is verified, it will allow us to understand the mechanisms of post-implantation autoimmune disease better and to devise special guidelines, if needed, for the follow-up of women with implant rupture.

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