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B Lymphocyte Mediated Immune Response to Silicone Breast Implants: A Short Commentary on a Systematic Review

Puja M. Jagasia, Iulianna C. Taritsa, Kazimir Bagdady and Megan Fracol*

Division of Plastic Surgery, Department of Surgery, Northwestern University-Feinberg School of Medicine, Chicago, IL, USA

Abstract

Silicone breast implants have been linked to the development of cancers such as Breast Implant Associated-Anaplastic Large Cell Lymphoma (BIA-ALCL) and lesser understood conditions Breast Implant Illness (BII). The pathogenesis of BIA-ALCL has been linked to T-cell activation and proliferation in the capsule of textured breast implants. The effect of silicone breast implants on B cell-mediated immune reactions is not broadly understood. To cultivate a better understanding of how breast implants, affect B-cell mediated immune responses, both local *in* the capsule and potentially systemically, the authors performed a systematic review. After screening 1096 articles, 39 studies met inclusion criteria. Of the 39 studies meeting inclusion criteria, 23 studied human subjects, 14 studied animal models and 2 studied *in vitro* models. These studies focused on B cell-mediated immune responses on either a systemic level by examining antibody formation or on a local level by examining the breast implant capsule. Common results included the presence of anti-silicone antibodies and autoantibodies frequently implicated in autoimmune diseases. B lymphocytes found in the breast implant capsule were shown to form germinal centers and plasma cells, which secrete antibodies. Importantly, ten studies showed no indication that B cell-mediated immunity was significantly different in breast implant exposed subjects compared to those without implants. Exposure to silicone breast implants can result in B-cell mediated immune responses such as antibody formation. More research is needed to link these findings to the clinical manifestations of breast implant associated pathology.

Keywords: B lymphocyte • B cell • Silicone • Breast implant • Antibody production

Description

Our group recently published an article titled "Systematic literature review of breast implant silicones and b cell-mediated immune responses" in the journal of plastic, reconstructive and aesthetic surgery open [1]. This article aims to provide an understanding of the interaction between silicone breast implants and the immune system with a focus on B lymphocytes and antibody formation. Silicone breast implants have recently been linked to the development of Breast Implant Associated-Anaplastic Large Cell Lymphoma (BIA-ALCL), Breast Implant Associated-B Cell Lymphoma (BIA-BCL) and a poorly understood phenomenon termed Breast Implant Illness (BII), which presents with symptoms such as fevers, arthralgias, hair loss, fatigue, chronic pain and more [2-4]. The pathogenesis of BIA-ALCL involves T-cell activation and proliferation in the capsule of textured breast implants [5]. However, the pathogenesis of BII and BIA-BCL remains unknown.

To cultivate a better understanding of how breast implants, affect B-cell mediated immune responses, both local in the capsule and potentially systemically, the authors performed a systematic review of both EMBASE and PUBMED in accordance with PRISMA guidelines. After screening 1096 articles, 39 studies met inclusion criteria [6-14]. Twenty-three papers used data from human patients, 14 papers were focused on *in vivo* animal models and 2 studies were conducted using *in vitro* human cell culture models (one of these studies included both *in vitro* and animal data) of the studies on humans, the majority (n=19) studied the systemic B cell response to silicone by quantifying, through multiple methods, the presence of anti-silicone antibodies and other auto-antibodies of interest [15-22]. Many of these studies found elevated anti-silicone antibodies and various autoantibodies, which can be found in Table 1. Notably, many of the autoantibodies that were reported to be elevated are implicated in autoimmune diseases, which share many symptoms with BII [23-30]. It should be noted that four studies found no increase in auto-antibody production between breast implant patients and non-breast implant controls [31-38].

***Address for Correspondence:** Megan Fracol, Division of Plastic Surgery, Department of Surgery, Northwestern University-Feinberg School of Medicine, Chicago, IL, USA; E-mail: mfracol@nm.org*

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Table 1: Autoantibodies found to be elevated in breast implant-exposed human serum.

Author (Year)	Elevated antibody
Bar-Meir (1995)	Anti-H2AH2B, HPRPP, SS-A, SS-B, Scl-70, CL, PS, GM2 and NC-1
Bridges (1993)	Anti-centromere, PM-Sci, BB' polypeptide
Brunner (1996)	Anti-thyroglobulin, microsomial
Cuellar (1995)	Anti-nuclear
Fracol (2021)	Anti-mammaglobin-A, mucin-1
Press (1992)	Anti-nuclear
Zandman-Goddard (1999)	Anti-SSB/La, collagen-II

The remainder of human studies (n=4) focused on the local immune response by examining the tissue capsule that forms around the implant. Looking at the capsule on a cellular level, the majority of lymphocytes are T lymphocytes, with only a minority of B lymphocytes [39-45]. B cells found in the capsule, however, are able to form reactive germinal centers and plasma cells (active antibody-secreting B cells). This suggests an adaptive immune response to the foreign body breast implant. Animal models confirmed that silicone can act as an antigen and induce B cell-mediated responses such as increased production of anti-silicone antibodies. It is important to note again that some studies (n=10) showed no indication that B cell-mediated immunity was significantly different compared to women without breast implants.

This evidence of B cell-mediated immune responses after exposure to breast implants begs the question; What other immune responses occur after a patient receives breast implants? After initial breast implants are placed, the host immune cell responses to the outer silicone shell drive the initial foreign body response, which results in the formation of a peri-implant capsule [46]. The foreign body response occurs almost immediately with the deposition of proteins such as fibronectin, IgG, complement and fibrinogen on the implant surface [46]. These proteins then activate the coagulation and complement cascades, which results in increased vascular permeability and the influx of macrophages and leukocytes [46]. Outside of the immune response to the implant's surface, there is evidence to support the release of particulate silicone debris, which is termed silicone gel bleed [47]. Macrophages take up the silicone debris then fuse to form giant cells and/or granulomas, which have been found in regional lymph nodes and in distant organs [48]. Macrophages act as the link between innate immunity and subsequent adaptive immunity when these phagocytosed antigens are subsequently presented to lymphocytes [48].

While many studies provide evidence that exposure to breast implants can alter immune responses, more research is needed to link these findings to the clinical manifestations of breast implant associated pathology. Breast implant illness remains a very controversial diagnosis in the medical community [49]. There have been multiple studies trying to find a biologic link between the vague symptoms and the breast implant, but to date no studies have been able to identify a definite biologic mechanism to account for patient symptoms [50,51]. Some of the studies included in this systematic review suggest that silicone breast implants may activate B cells in the peri-implant capsule, which can have systemic effects on the production of antibodies against silicone and autoantibodies. Most importantly to note, most of these studies were performed in the 1990s and early 2000s, when the ban on silicone breast implants was in place and heightened research interest existed [52]. There are essentially no modern studies on this subject and we, as the authors of this systematic review, hope to re-invigorate public interest in researching this topic. Silicones are not only found in breast implants, but are ubiquitous in implanted medical devices and as such this topic has far-reaching implications for all types of patients [53].

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