The Dark Side of Beauty: About Breast Implants and Lymphoma

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Since the first silicone gel-filled breast implant was performed by Cronin and Gerow in 1962 [1], this procedure has become common practice, and to date about 10 million women worldwide have benefited from this operation for aesthetic or reconstruction purposes. Breast implants consist of a smooth or textured silicone envelope filled with silicone gel or isotonic saline. They contain a type of medical silicone called polydimethylsiloxane.

Silicone was thought to be an ideal inert substance, causing no inflammation, immunogenicity or carcinogenesis [2]. However, from the first use of these prostheses, localized and distant granulomatous reactions were observed due to leakage of silicone micro-particles through the implant's envelope (also called "silicone bleeding") demonstrating the immunogenic potential of silicone [2-5]. These micro-particles are thought to be captured by macrophages in the surrounding tissue and lymph nodes, thereby causing an inflammatory reaction with cytokine production and immune cell recruitment [2,3].

Regarding the oncogenic risk, large studies and meta-analyzes did not find an increased risk of breast cancer in women with breast implants [6,7]. Nevertheless, since the first report by Keech and Creech in 1997 [8], several dozen cases of primary breast anaplastic large cell lymphoma (ALCL) associated with mammary prostheses have been described [9,10]. In the June 2017 issue of IMAJ, Ben-Nun et al. [11] reported the first Israeli case of ALCL thought to be caused by a breast implant.

Breast ALCL is a rare lymphoproliferative disorder, accounting for 0.5% of all breast cancers. However, a growing number of cases have been reported in recent years, probably due to the widespread use of breast prostheses and to an increased knowledge of this entity, which is leading to better diagnosis. Interestingly, this T-cell non-Hodgkin's lymphoma strongly expresses CD30-positive markers and has negative anaplasic lymphoma kinase (ALK) gene expression [10]. This clinicopathologic profile of mammary lymphoma is exclusively related to the presence of breast implants [2,10]. Indeed to date, it has never been observed without mammary prosthesis. This specific relationship suggests an oncologic mechanism directly linked to the presence of the prosthesis and its components, and therefore, could present a unique opportunity to analyze how mammary implants might influence the immune system, leading to the development of malignant clones.

Chronic infection and inflammation have long been seen as a causative mechanism in the development of lymphoma. Some infectious agents responsible for chronic infection can promote malignant processes. Thus, human herpesvirus-8 (HHV8), Epstein-Barr virus (EBV), human T-cell leukemia-lymphoma virus type 1 (HTLV-1) and *Helicobacter pylori* have been related to the development of lymphoma (Kaposi's sarcoma, Hodgkin's lymphoma, T-cell lymphoma and mucosa-associated lymphoid tissue lymphoma [MALT], respectively) [2].

Similarly, chronic stimulation of the immune system occurring in autoimmune diseases may lead to an increased risk of lymphoma. Typical examples include patients with rheumatoid arthritis and/or lupus, who exhibit a two- and threefold increased risk of lymphoma [12]. The highest risks are observed in Sjögren syndrome and Hashimoto thyroiditis patients, who have a 16- and 60-fold increased risk [12]. Regarding the classic example of Sjögren's syndrome, patients present polyclonal B-cell activation, probably due to chronic stimulation by exoantigens and autoantigens, inducing cytokines and autoantibody production. The transition toward a monoclonal lymphoproliferation is still poorly understood, but likely involves several oncogenic events, such as microsatellite instability, loss of cell cycle control of B-cells and forced overproduction of specific B-cell biologic stimulators [2].

The pathogenesis of breast implants associated with ALCL is thought to be similar, implying chronic stimulation of the immune system.

It is important to note that in the majority of cases, lymphoma develops in the peri-prosthetic capsule. Indeed, after the installation of the prosthesis, an inflammatory reaction leads to the cicatrization of the surrounding tissue, resulting in the constitution of a fibrotic capsule around the implant. Most ALCL cases occur in the space between the scar capsule and the implant, usually manifesting by the appearance of a seroma [Figure 1], as in the case reported by Ben-Nun et al. (11). This particular localization suggests a direct inter-

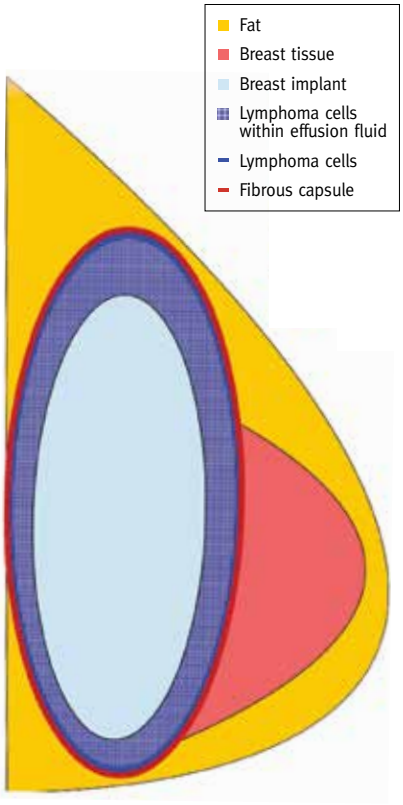
action between the prosthesis and immune cells resulting in their transformation. As such, several physiopathological hypotheses have been proposed.

As mentioned earlier, silicone has been found to induce immunogenic reactions. Indeed, micro-particle leakage can result in granuloma formation by activating macrophages and inflammasomes [12]. More generally, silicone is thought to act as an adjuvant, that is, a substance able to enhance, accelerate or prolong an antigen-specific immune response [13]. Thus, it has been shown to activate a Th1/Th17 immune response, participating in the peri-capsular fibrosis, and maintaining chronic inflammation [2,4]. Conversely, some case studies have reported remission of local and systemic manifestations after prosthesis explantation [4]. In light of these observations, some authors have surmised that mammary implants may cause an autoimmune/inflammatory syndrome induced by adjuvants (ASIA syndrome or Shoenfeld's syndrome) [4,12]. Described in 2011 by Shoenfeld and Agmon-Levin [14], this syndrome encompasses various medical conditions triggered by exposure to an adjuvant. Consequently, silicone could lead to an immune system activation, autoantibody formation and polyclonal hypergammaglobulinemia [2]. Moreover, recent advances have suggested that long-lasting exposure to adjuvants may not only trigger autoimmunity, but also may progress to monoclonality of chronic inflammation, thus resulting in the development of hematologic malignancies such as lymphomas [2,12]. Breast implants associated with ALCL could therefore be an evolution of an inflammatory state induced by silicone.

Other causal factors have been discussed. Most ALCL occurs on textured prostheses, as opposed to smooth implants, suggesting an immunologic response to chronic irritation by the textured surface [10,15]. Bacteria may also be a cause of ALCL development. Some studies have found a gram-negative bacteria biofilm on some implants, particularly on textured implants. These bacteria were associated with an increased T-cell response with the number of lymphocytes being proportional to the number of bacteria [10,15]. Indeed, bacterial cell wall components are potential stimulators of immune cells, notably through toll-like receptors activation. Genetic background could also play a role in ASIA syndrome, as suggested by Perricone and colleagues [16]. In addition, oncogenic mutations activating STAT3 were found by Laurent et al. [15].

These different hypotheses would explain why in the majority of ALCL the removal of the prosthesis is sufficient to treat the lymphoma, that is, the agent maintaining the chronic inflammatory reaction is removed. In addition, remission after removal of the prosthesis, and therefore of the stimulating agent (silicone), is a major criterion for suggesting that the ALCL associated with breast implants is part of the ASIA syndrome.

Figure 1. Development of beast anaplastic large cells lymphomas (ALCL) in the effusion fluid (seruma) between breast implant and fibrous capsule



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