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Review article

Silicone implants and lymphoma: The role of inflammation

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ABSTRACT

The risk of hematological malignancies is mainly determined by genetic background, age, sex, race and ethnicity, geographic location, exposure to certain chemicals and radiation; along with the more recently proposed immune factors such as chronic inflammation, immunodeficiencies, autoimmunity, and infections. Paradigmatic examples include the development of lymphoma in Sjögren's syndrome and Hashimoto thyroiditis, gastric MALT lymphoma in *Helicobacter pylori* infection, or lymphomas associated with infections by Epstein–Barr virus, human herpes virus 8 (HHV 8) and leukemia/lymphoma virus 1 (HTLV-1). A growing number of reports indicates an increased risk of lymphoma, particularly of the anaplastic large cell (ALCL) type. The implants, specifically those used in the past, elicit chronic stimulation of the immune system against the prosthetic material. This is particularly the case in genetically susceptible hosts. We suggest that polyclonal activation may result in monoclonality in those at risk hosts, ultimately leading to lymphoma. We suggest that patients with an inflammatory response against silicone implants be monitored carefully.

Contents

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1. Introduction

Materials used as implants were developed with the purpose to be chemically inert, exhibit temperature stability, resistance to oxidation, microorganisms, mechanical strain, and body fluids. Additionally they are to cause no inflammation or hypersensitivity, maintain their shape, be amenable to sterilization, and should not be carcinogenic [1]. Silicone was the first material believed to display such features and was originally used as a human medical implant in 1946 for the repair of large bile ducts [2]. Silicone is currently found in numerous devices used in medical practice: including breast and larynx implants, elastomeric toe and finger joints, hydrocephalus shunts, implantable infusion pumps and ports, tissue expanders, intraocular lenses, pacemaker and defibrillation devices, penile and testicular prostheses [3]. The effects of silicone on chronic inflammation must also take into account the numerous factors proposed to facilitate tolerance breakdown and autoimmunity development in women [4,5] and the genetic and epigenetic susceptibility [6–8].

2. Silicone

Silicones refer to a large family of organic silicone polymer products with a main chain of alternating silicon and oxygen atoms. Typically, each silicon in the chain carries two methyl groups and the material is called polydimethylsiloxane (PDMS), seen in Fig. 1. The physical and chemical properties of the polymer are determined by the chain length, with longer chains more viscous than shorter ones. Further vulcanization of the polymer crosslinks individual chains and, depending on the degree of crosslinking, the resultant silicone varies in consistency from a clear white fluid to a gel or an opaque elastomer. Extensively crosslinked polymer can be further compounded with fumed silica to impart additional resistance to the material [2,3,9,10]. Silicone leakage, also defined as 'silicone bleeding', represents the migration of relatively low molecular weight silicone compounds through the implant's elastomer envelope [3,11]. It is postulated that this might be due to physical migration or engulfment and transport of silicone microdroplets by macrophages in the surrounding tissue and lymph nodes [12,13]. Silicone leakage is observed with any type of silicone prosthesis including those of the breast, joint, genitourinary system and intravitreal oil tamponade [1,14–19]. Leaked silicone may cause a histiocytic reaction with foreign-body giant cells forming granulomas ('siliconomas') even in distant sites such as the skin, lungs, nerves, legs, face, salivary glands, bone marrow, and vulva [20–29]. Alternatively, illegal techniques (i.e. injection of liquid silicone, oil paraffin, polyacrylamide hydrogel and unidentified liquid gels) are used in certain geographical areas for breast, buttock and penile augmentation. Liquid silicone is a synthetic polymer incorporating oxygen and the semimetallic element silicon and is currently approved by FDA only for specific ophthalmologic indications. It may induce tissue necrosis, foreign-body giant cell reactions and infection at the site of injection. Liquid silicone migration may also ensue and manifest with lymphadenopathy, granulomatous hepatitis, interstitial nephritis, and pneumonitis [12,30–34].

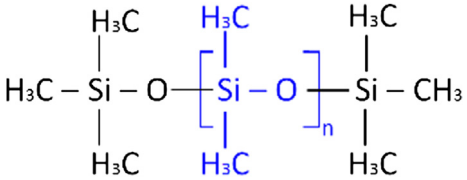

Fig. 1. Polydimethylsiloxane (PDMS). C: carbon, H: hydrogen, O: oxygen, Si: silicon, n: number of repeating units.

3. Breast implants

Breast implants are performed for either esthetic reasons or reconstruction following mastectomy. Since the introduction of silicone gel prosthesis in 1962 by Cronin and Gerow, breast augmentation has become the most commonly performed operation in cosmetic surgery [35]. It has been estimated that this procedure has been performed on over 10 million women worldwide [36]. Breast implants contain a type of medical silicone called polydimethylsiloxane (PDMS) and can be further classified as: (i) silicone rubber envelopes filled with saline, (ii) silicone rubber envelopes filled with silicone gel, (iii) silicone rubber envelopes covered with polyurethane foam coating, (iv) dual silicone rubber envelopes, with the inner envelope containing silicone gel and the outer envelope filled with saline [22,37]. The external surface of the implants may be smooth or textured and is specifically designed to reduce the risk of leakage of low-molecular-weight silicone. Nonetheless, gel fluid diffusion can be as high as 300 mg per year, particularly for older implants [38]. It has been demonstrated that most prostheses lose the integrity of their silicone shell after 8–14 years [1,22,39].

4. Primary breast lymphomas

Lymphoma is a rare form of primary breast malignancy, accounting for 0.04–5% of all breast tumors and approximately 1.7% of extranodal lymphomas which may be found in the skin (21%), soft tissues (17%), bone (17%), lungs (11%), and liver (8%) [40–49]. The majority (~90%) of breast lymphomas are of B-cell origin; T-cell lymphomas however are predominantly peripheral. Anaplastic large cell lymphoma (ALCL) accounts for 3% of newly diagnosed non-Hodgkin cases [43,44,50–53] and its diagnosis is based on established criteria summarized in Table 1.

Chronic infection and inflammation have been implicated as the causative mechanisms in the development of lymphomas. The following are of particular relevance: Sjögren's syndrome and Hashimoto thyroiditis, gastric MALToma in *Helicobacter pylori* infections, as well virally associated lymphomas of HHV8, EBV and HTLV-1 and proposed associations are summarized in Table 2.

The World Health Organization classifies ALCL into primary cutaneous and primary systemic forms. Primary cutaneous ALCL manifests as an indolent course and is associated with a 90% 5-year survival. Anaplastic lymphoma kinase (ALK) expression in primary cutaneous ALCL is generally negative; skin lesions often regress spontaneously but may recur after treatment with single–agent chemotherapy or radiotherapy. Chronic inflammation of the skin appears to play a role in the development of cutaneous lymphoma, additionally similar roles for insect bites and foreign bodies have been proposed [54]. Primary systemic ALCL accounts for approximately 2–3% of all adult forms and 12% of T-cell non-Hodgkin's lymphomas. Primary systemic ALCL tend to occur in

Table 1
Diagnostic criteria for anaplastic large cell lymphoma (ALCL) [45].

Minimal criteria for ALCL
1. Malignant cytology (abnormal nuclei, prominent nucleoli)
2. Strong uniform expression of CD30
3. Exclusion of epithelial malignancies (cytokeratin-negative)
Additional criteria
- Documentation of the t(2; 5) chromosomal translocation
- And/or anaplastic lymphoma kinase protein overexpression
- Clonal rearrangement of the T-cell receptor gene