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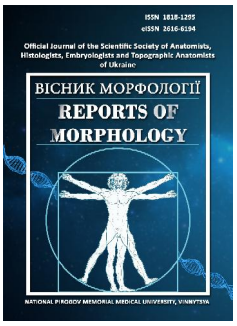

Stromal-cellular remodeling of breast tissue after silicone implant damage

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One of the current vectors of modern reconstructive and cosmetic surgery is augmentation mammoplasty - an operation to enlarge the mammary glands. The breast implant is well tolerated by the body, as the immunogenicity of its material is extremely low. At the same time, the silicone gel of the implant is a foreign object and the surrounding breast tissues give a stereotypical response in the form of growth of the connective tissue stroma with the formation of a capsule around the implant and the appearance of focal cellular infiltrates. Modern breast implants, unlike implants of previous decades, are more sophisticated in their structure, and the level of protection against damage is much higher. A complication associated with the long-term use (up to 20 years) of implants, where low-quality silicone or industrial silicone was used as a filler, is the penetration of low-molecular-weight particles of the implant through its shell to the surrounding tissues with the subsequent formation of silicone granules. In the vast majority, such changes develop after mechanical traumatization of the implant. The purpose of the study is to establish the morphological criteria of the reaction of breast tissue after silicone implant damage. The material for research was histological micropreparations of breast tissue from the archive of the "Grace Clinic" (Kyiv), with the mutual consent of patients who applied for repeated mammoplasty. The duration of the implants in the breast gland was from 6 to 20 years. The age range of the women was from 36 to 53 years. On preparations stained with hematoxylin and eosin, tissue biopsies of the glands of 9 patients with a diagnosis of deformation of silicone implants and violation of the integrity of their wall were presented. The micropreparations were visualized using a UlabXSP-137TLED light microscope at various magnifications and photographed with an XCAM 1080P camera. The study of histological preparations of soft tissues of the breast glands, from which silicone implants were removed, established changes in stromal-cellular elements, namely: decorated fibrous structures accumulated in the form of dense capsules with elements of local contractures; from the side of cellular elements, the most demonstrative were cellular infiltrates, which included macrophages, lymphocytes, and plasma cells, which indicated a high probability of a chronic inflammatory process. A large number of giant multinucleated cells of foreign bodies were present in practically all examined sections, which indicated the impossibility of macrophages to complete phagocytosis with lysis of the phagocytosed material, which by its chemical composition is the silicone of the implant. All the described phenomena can be interpreted as a natural reaction of the tissues to the implant, the contents of which got into the soft tissues of the breast. Thus, the presence of numerous giant multinucleated cells of foreign bodies, dense capsules with elements of local contractures, and a significant predominance of macrophages, lymphocytes, and plasma cells in cellular infiltrates over other cellular elements can be considered a morphological criterion for the reaction of breast tissue to silicone implant damage.

Keywords: *mammary/breast gland, breast implant, breast silicone implant damage, aesthetic surgery, microscopy, histopathological diagnosis, implant-associated fibrotic changes.*

Introduction

One of the relevant vectors of modern reconstructive and cosmetic surgery is augmentation mammoplasty - an operation to enlarge the mammary glands, which is most often chosen by patients [1, 20]. As a rule, the breast implant is well tolerated by the body, since the immunogenicity of its material is extremely low. At the same time, the silicone gel of the implant is a foreign object [22, 23, 32, 40]. Therefore, when it is installed, the surrounding tissues of the breast gland make a stereotypical response in the form of growth of the connective tissue stroma with the formation of a capsule around the implant and the appearance of focal cellular infiltrates [2, 10, 19, 26]. A complication of such phenomena can sometimes be the formation of Baker grade IV capsular contracture, which gives the gland incredible hardness and a bad aesthetic appearance [5, 37, 45]. In the scientific literature, there are descriptions of complications associated with the use of industrial silicone as an implant filler, which often occurred at the beginning of the development of breast implantation [10, 28, 30, 38]. In such cases, the penetration of low-molecular-weight particles of the implant through its shell to the surrounding tissues with the subsequent formation of silicone granulomas was observed [14, 16]. The authors of these studies note that most often such changes develop after mechanical damage to the implant, mainly as a result of trauma.

The scientific literature also contains data on other morphological variants of the reaction of breast tissue to the implant [11, 31, 34]. The most common among them is synovial metaplasia (transdifferentiation) [7, 27], in which epithelioid cells similar to synovial cells appear on the inner surface of the fibrous capsule bordering the implant, and in general, this structure resembles a joint [28]. In cases of mechanical damage to the implant, the formation of silicone granulomas, which are represented by multiple cystic spaces filled with silicone spherules, is not excluded. On the periphery of such spaces, fibrosis and a macrophage reaction with the formation of giant multinucleated cells of foreign bodies is observed. Such changes occur, as a rule, with extracapsular rupture of a silicone implant with a violation of the integrity of the fibrous capsule [16].

Modern breast implants, unlike implants of previous generations, are more sophisticated in their structure, and their level of protection against damage is much higher [28]. However, if injuries occur, clinical symptoms are minimal, with a relatively favorable prognosis for the occurrence of significant pathomorphological changes.

The purpose of our study was to establish the morphological criteria of the reaction of breast tissue after silicone implant damage.

Materials and methods

The work was approved at a meeting of the Bioethics Commission of Danylo Halytsky Lviv National Medical University; Protocol № 7 dated 26.06.2023 on compliance with the basic bioethical provisions of the Council of Europe Convention on Human Rights and Biomedicine (dated 04.04.1997), the Helsinki Declaration of the World Medical Association on Ethical Principles of Scientific Medical Research with Human Participation (1964-2008), and also the Order of the Ministry of Health of Ukraine № 690 dated 23.09.2009.

The material for the research was histological micropreparations of breast tissue from the archive of the "Grace Clinic" (Kyiv) with the mutual consent of patients who applied for repeated mammoplasty. Treatment included removal of damaged implants, capsulotomy due to the development of capsular fibrosis, and repeat mammoplasty.

According to the anamnesis, all patients were healthy, and none of them had signs of an autoimmune disease or other connective tissue pathology. The duration of the implants in the gland was from 6 to 20 years, and the age range of the women was 36-53 years.

A morphological study of the removed tissues was carried out. On preparations stained with hematoxylin and eosin, tissue biopsies of breast glands of 9 patients with a diagnosis of deformation of silicone implants and violation of the integrity of their wall, presence of capsular contracture are presented. On the basis of the Department of Histology, Cytology and Embryology of the Danylo Halytsky Lviv National Medical University, micropreparations were visualized using a UlabXSP-137TLED light microscope at various magnifications and photographed using an XCAM 1080P camera.

The identified morphological features of changes in the fibrous capsule were assigned to one of four types (I-IV) according to the classification of Wilflingseder et al. (1983) [8, 44], which is consistent with Baker's classification, which is used in clinical practice [1, 11, 12, 29].

Morphological criteria of breast tissue response to the implant and changes in the fibrous capsule, according to the classification of Wilflingseder et al. (1983) included a thin, loose capsule (type I), "constrictive fibrosis", absence of foreign body giant cells (type II), "constrictive fibrosis", presence of foreign body giant cells (type III), presence of inflammatory cells, foreign body granulomas, neovascularization, neuromas (IV type) [44].

Results

When studying the micropreparations, we discovered a number of changes that occurred as a result of the reaction of the gland tissues to the presence of the implant. Although the architecture and morphology of the formed fibrous capsules around the implant had a similar histological structure, they were characterized by certain differences. In all investigated cases, the capsules had a three-layer, similar histological structure. The inner layer, which was located closer to the implant, was represented by a single- or multi-layered epithelium with the presence

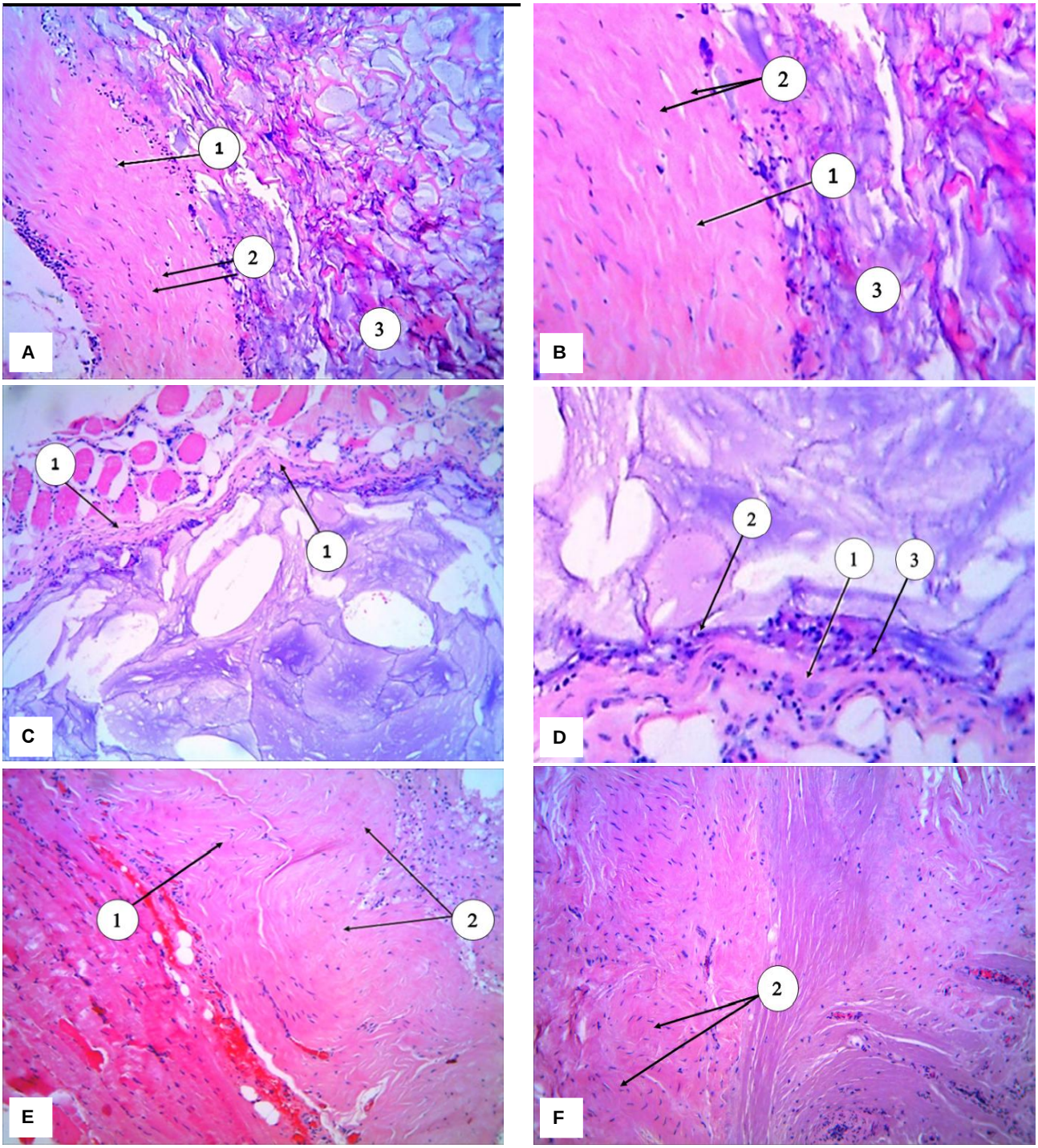

Fig. 1. Architectonics and morphology of the fibrous capsule of the breast tissue in the presence of the implant: A and B: 1 - thick fibrous capsule with a predominance of the fibrous component, 2 - parallel orientation of collagen fibers around the gel areas, 3 - gel areas. Hematoxylin-eosin. x100 (A), x400 (B); C and D: 1 - a thin connective tissue capsule around the areas of the gel, which corresponds to the 1st type according to Wilflingseder, 2 - an inflammatory cell infiltrate with a predominance of lymphocytes and plasma cells (3). Hematoxylin-eosin. x100 (C), x400 (D); E and F: 1 - wavy orientation of collagen fibers, 2 - thick bundles of collagen fibers arranged concentrically (capsular contracture). Hematoxylin-eosin. x100 (E and F).

of fibroblasts and macrophages, in isolated cases it looked like a pseudo-epithelial layer with synovial metaplasia. The middle layer was formed by loose connective tissue with widened lumens of thin-walled vessels and high cell density. The outer layer was formed by dense collagen tissue and the surface layer of blood vessels. The thickness

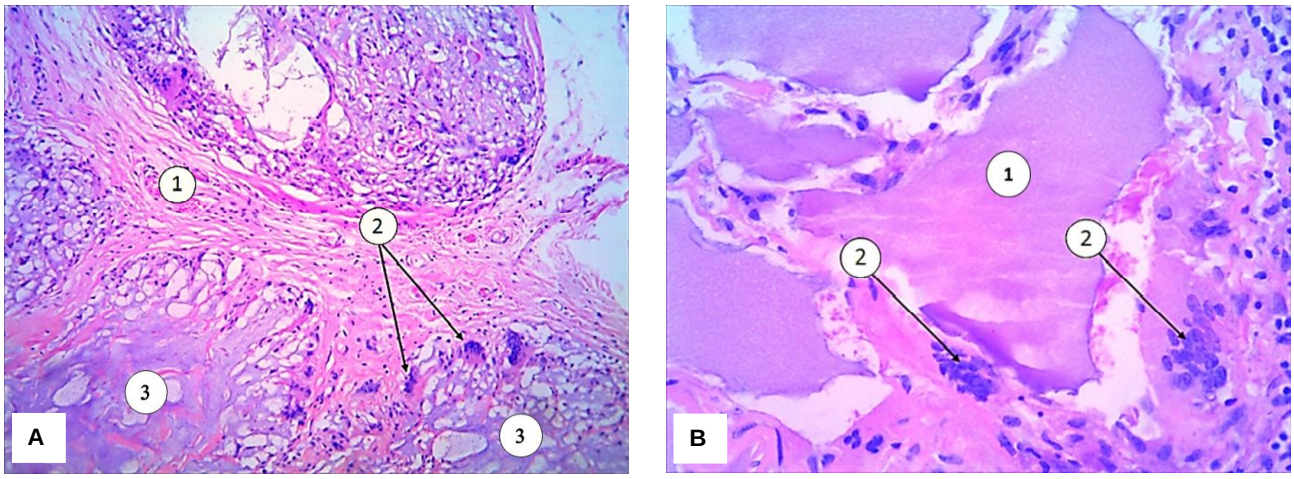

Fig. 2. Cellular response to contact with silicone gel. A: 1 - pronounced fibrous capsule around areas of gel, 2 - giant multinucleated cells of foreign bodies type, 3 - areas of gel. Hematoxylin-eosin. x100; B: 1 - areas of gel, 2 - giant multinucleated cells of foreign bodies type. Hematoxylin-eosin. x400.

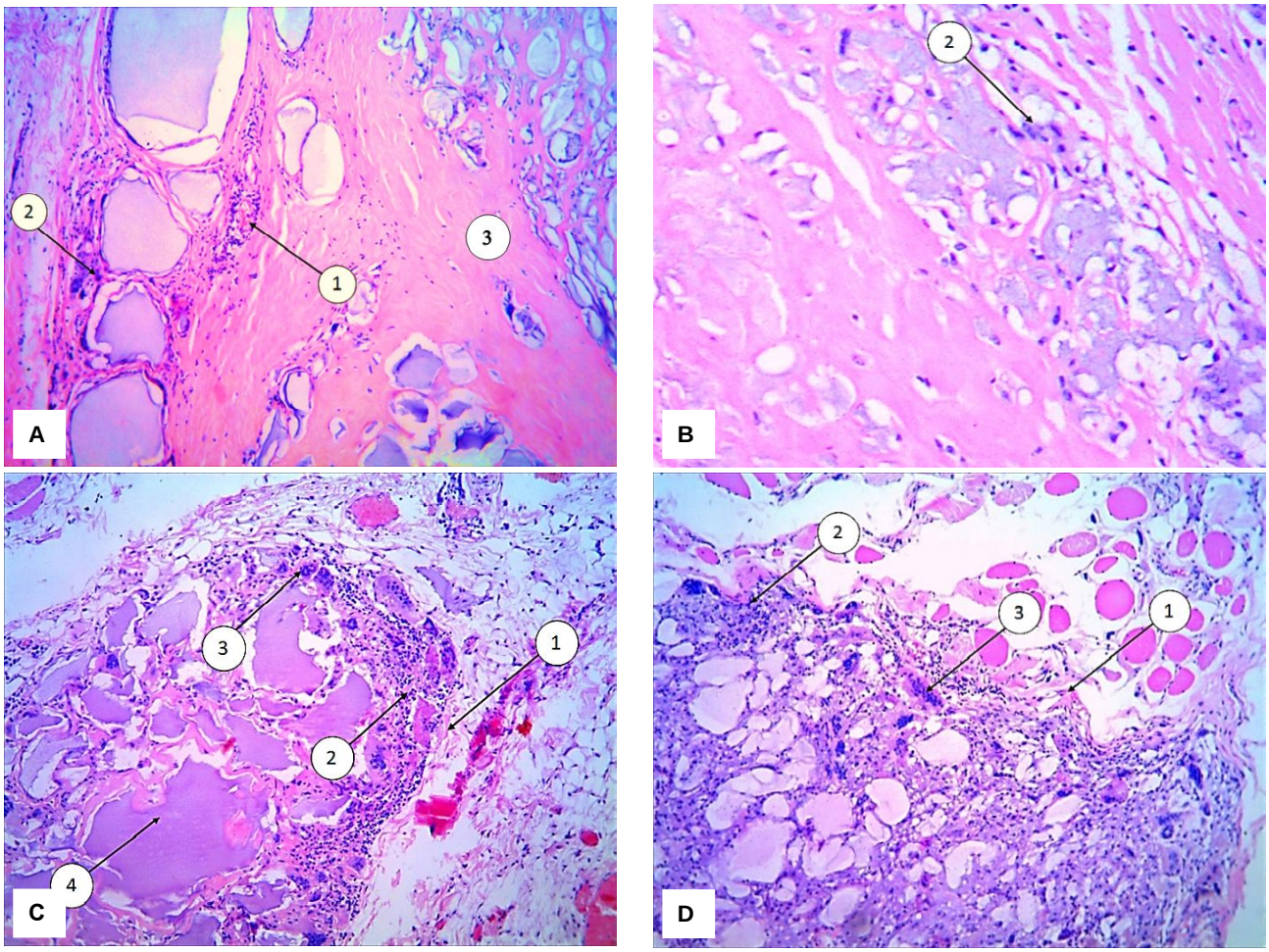

Fig. 3. Inflammatory cell infiltrate in the tissues of the breast upon contact with silicone gel of varying severity. A and B: 1 - slight inflammatory cell infiltrate with a predominance of lymphocytes and plasma cells, located perivascularly, 2 - infiltrate around the gel areas, 3 - thickened fibrous tissue with hyalinosis around the gel areas; C and D: 1 - pronounced inflammatory cell infiltrate with a predominance of lymphocytes and plasma cells, 2 - giant multinucleated foreign body-like cells, 3 - thin fibrous capsule around the gel areas, 4 - gel areas. Hematoxylin-eosin. x100 (A, C, D), x400 (B).

of the capsule varied from 2 to 8 mm, on average it was equal to 4-5 mm. Capsule thickness was measured at the thickest point of the capsule.

During the microscopic examination of preparations

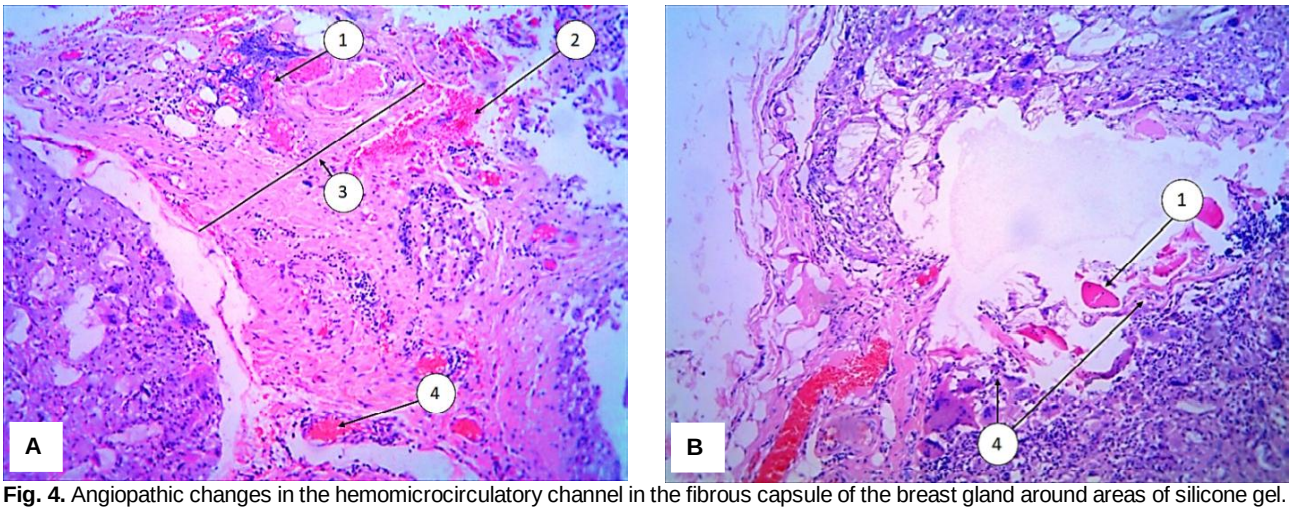

Fig. 4. Angiopathic changes in the hemomicrocirculatory channel in the fibrous capsule of the breast gland around areas of silicone gel. A, B: 1 - foci of angiomatosis, 2 - hemorrhages in the fibrous capsule, 3 - fibrous capsule, 4 - numerous thin-walled newly formed capillaries surrounded by inflammatory infiltrate. Hematoxylin-eosin. x100.

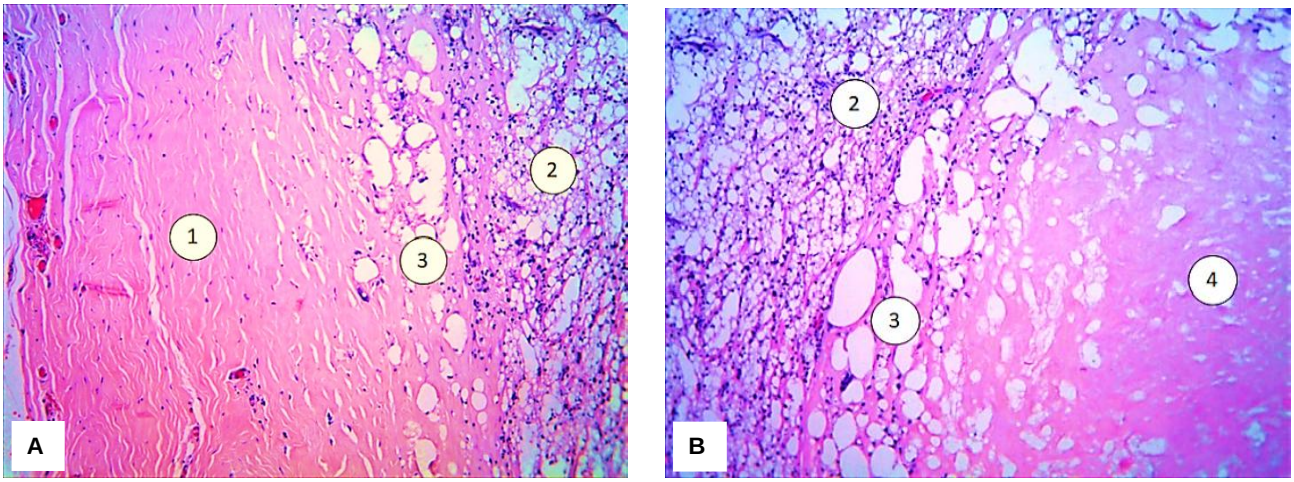

Fig. 5. The reaction of fatty connective tissue of the breast gland to the presence of silicone gel. A and B: 1 - thick fibrous wall after plastic surgery with a silicone implant, 2 - numerous groups of "light" foamy macrophages, 3 - areas of fat necrosis, 4 - area with gel masses next to fat necrosis of adipocytes. Hematoxylin-eosin. x100.

stained with hematoxylin-eosin, we analyzed in detail the morphological features of changes in the fibrous capsule in the presence of capsular contractures. Attention was paid to the structure of collagen fibers, the density of their location, the number and size of cell nuclei, the presence of lymphocytes and macrophages, macro- and microparticles of silicone, the presence of giant cells of foreign bodies and granulomas of foreign bodies, the severity of the inflammatory reaction and its differentiation (acute or chronic), localization of inflammation (focal, diffuse, perivascular, near the implant), the presence of a synovial cell layer, signs of necrosis, calcification, bleeding.

Differences in the histomorphological picture between the samples were established, including variations in cellularity, organization and density of fibers, vascularization and general structure. The location of collagen fibers in some cases was mainly oriented parallel to the capsule. Between the fibers, numerous spindle-shaped cells, which morphologically had the characteristics of myofibroblasts, could be seen. In general, cellularity decreased from the inner to the outer layer, with the outermost layer distant from the implant having few cells and mostly collagen fibers. However, in some cases, we diagnosed areas near or at the border of the implant capsule with increased or concentrated cellularity, although the capsules generally had low cellularity.

Specimens with a thickened fibrous capsule (II-IV types) predominated (Fig. 1 A, B), only in one case there was a thin non-compacted capsule, which corresponded to type I according to Wilflingseder (Fig. 1 C, D). In the composition of thickened fibrous capsules, in most cases, the correct orientation of collagen fibers was disturbed, bundles of collagen fibers were found, located concentrically and separated by individual fibroblasts and fibrocytes, which was a sign of the formation of capsular contracture (Fig. 1 E, F). Especially such changes in the orientation of collagen fibers were diagnosed in cases of damage to the implant wall and the release of the gel. The histological pattern in a

number of samples also drew attention, when the capsules consisted of one collagen layer of altered density with hyalinosis.

In all studied samples, the material of silicone granules was found surrounded by resident cells of connective tissue and migrant cells, which reacted locally in the form of clusters of macrophages with the formation of so-called giant multinucleated cells of foreign bodies (Fig. 2).

Morphological criteria of breast tissue reaction to the implant included the presence, in addition to giant multinucleated foreign body-type cells, as well as an inflammatory cell infiltrate of varying severity with a predominance of lymphocytes, plasma cells, and "light" foamy macrophages (Fig. 3). Increased accumulation of macrophages with intracellular silicon in the form of microparticles was revealed. In addition, polygonal cavities of different sizes were observed, as well as accumulation of more rounded cavities due to dissolved silicone. The number of silicone particles significantly decreased along the periphery of the implant.

In most cases, the area of the capsule adjacent to the implant had no vascularization, although it was evident throughout the capsule in a small number of specimens. Angiopathic changes in the hemomicrocirculatory channel were recorded in almost all cases. Individual vessels were dilated, and their walls were thickened, with the presence of oxyphilic amorphous masses in the lumens. Hemorrhages localized in the inner and middle layers of the capsule, as well as numerous thin-walled capillary neoplasms surrounded by inflammatory cells, were found in two samples (Fig. 4).

Certain groups of adipocytes of adipose connective tissue also underwent changes. Such cells decreased in size, lost their traditional shape, and sometimes underwent necrobiotic changes. Areas of fat necrosis were diagnosed (Fig. 5).

Discussion

To date, more than a million breast augmentation procedures using breast silicone implants have been performed in the world. A potential risk with a stable implant is still the possibility of rupture of its capsule with infiltration of silicone into the surrounding tissues and the occurrence of a number of side effects that cause discomfort or pose a threat to health. These include such local complications as pain, swelling, redness, infections, capsular contracture, implant rupture, and gel "bleeding" [9, 16, 17].

The increasing number of patients with breast implants has in turn increased the likelihood of less common complications, which include seromas or late infection, breast lymphadenopathy, granulomas in the implant capsule, which in some cases can extend beyond the fibrous capsule, desmoid tumors and large cell anaplastic lymphoma [13, 39].

The main atypical complications associated with breast implants relate to late seroma [13, 41] and the diagnosis of large cell anaplastic lymphoma [25, 38]. In addition, patients experience systemic symptoms such as chronic fatigue, arthralgias, myalgias, fever, and even cognitive dysfunction. These symptoms have been given various names such as adjuvant-induced autoimmune/ autoinflammatory syndrome due to silicone incompatibility syndrome and breast implant disease. Due to chronic immune activation, patients may develop allergies, autoimmune diseases, immune deficiencies, and, finally, lymphomas [19, 43].

Capsular contracture, based on our study and according to the data of many authors [3, 35], was the main risk for revision operations after aesthetic breast augmentation with breast implants. For example, Henriksen T. F. and co-authors [21] in 2005 found about 22% of capsular contracture as a complication after aesthetic breast plastic surgery. According to other authors, it has been established that fibrosis and capsular contracture in breast implants is a very dynamic process that does not depend on the age of the patient and the length of time the implants have been in place [26, 33]. K. Benediktsson and L. Perbeck [6] showed in their work that capsular contracture occurred during the first years in more than half of the patients. In our study, most patients developed capsular contracture in the first 3-5 years after implantation. But in some cases, the contracture did not manifest itself for many years. We could not establish cause-and-effect relationships. There is also a debate in the literature regarding the timing of capsular contracture, and according to the authors, the reasons for this have not been clarified [36].

There are various theories regarding the causes and pathomechanism of capsular contracture of breast implants, most of which consider the development of an inflammatory reaction with the induction of increased fibrosis and compaction of the capsule as the central mechanism [31]. Foreign body reaction or periprosthetic bacterial contamination are also discussed as potential triggers of the inflammatory response [4].

There are works in which it is shown that macrophages loaded with silicone play the main (central) role, stimulating fibroblasts to collagenogenesis and thus contribute to the development of capsular contracture [18, 24]. Macrophages in culture can be stimulated by silicone to release interleukin-1, which is a pro-inflammatory cytokine that plays an important role in fibroblast proliferation and differentiation [18, 42].

The results of research in recent years by Hernandez J. L. et al. [22] show conflicting opinions regarding the reaction to a foreign body: the question arises whether it is a non-specific reaction of the body or a specific activation of the immune system, whether it is the surface of the implant or particles of the surface that cause the corresponding reaction, or whether the filling of the implant, which is in contact with the body tissue due to leakage of its contents.

Thus, Dziubek M. and co-authors [15] demonstrated the results of research on silicone shells of breast

implants. Silicone gel implants showed "bleeding" of silicone particles into the periprosthetic capsule, an average of 1 million silicone particles per 1 capsule. On the other hand, no release of silicone particles was observed with saline breast implants. These data indicate that the release of particles occurs from the inner silicone gel and not from the smooth outer silicone shell.

However, Dijkman H. B. and co-authors [14], who studied saline breast implants, indicated that there are cases of silicone migration from the shell of saline breast implants, but they are very rare. The authors describe a unique case of a 66-year-old female patient with silicone migration from intact saline breast implants. The patient showed a number of symptoms indicating breast implant disease. X-ray data indicated the presence of silicone in the axillary lymph nodes, despite the integrity of the implants, confirming silicone migration. Histopathological examination revealed a reaction to a foreign body and the presence of silicone in the axillary lymph nodes. Given the salt content, the source is likely the polydimethylsiloxane breast implant shell. The rarity of documented silicone migration from intact saline breast implants, particularly in patients with breast implant disease, highlights the need for additional research into the health implications of silicone particle leakage.

It should also be taken into account that silicone implants are constantly being improved since their appearance, and a comparison between implants of different generations is impossible. There are no long-term studies on the latest generation of high-cohesive gel implants. Most of the research concerns old implants. In addition, each implant manufacturing company uses its own composition and constantly improves it.

Thus, patterns of local morphologic responses on breast implants may be of great importance as a possible starting point for the controversially discussed silicone-induced systemic immune response.

Only systematic registration of morphological reactions in the "prosthetic passport" along with additional dispensary monitoring of patients will be able to provide a realistic assessment of potential health risks for women with silicone breast implants in the future.

Conclusions

1. In the soft tissues of the mammary glands, from which silicone implants were removed according to clinical indications, a number of changes affecting, first of all, stromal-cellular elements were detected.

2. Regarding the stromal component, the accumulation of structured fibrous structures in the form of dense capsules with elements of local contractures was noted. In terms of cellular elements, the most demonstrative were cellular infiltrates, which included macrophages, lymphocytes, and plasma cells, which indicates a high probability of a chronic inflammatory process.

3. The most significant manifest sign revealed on histological preparations is a large number of giant multinucleated cells of foreign bodies, which obviously indicates the inability of macrophages to complete phagocytosis with lysis of the phagocytosed material, which by its chemical composition is the silicone of the implant.

4. The detected changes can be interpreted as a natural reaction of the tissues to a foreign object, in particular - an implant, the material of which has penetrated the soft tissues of the breast for one reason or another.

5. The risk of implant-related changes increases with prolonged implantation duration.

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СТРОМАЛЬНО-КЛІТИННА ПЕРЕБУДОВА ТКАНИН ГРУДНОЇ ЗАЛОЗИ ПІСЛЯ УШКОДЖЕНЬ СИЛІКОНОВОГО ІМПЛАНТА

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Одним з актуальних векторів сучасної реконструктивної та косметичної хірургії є аугментаційна мамопластика - операція зі збільшення грудних залоз. Грудний імплант толерується організмом добре, оскільки імуногенність його матеріалу є надзвичайно низькою. Водночас силіконовий гель імпланта є чужорідним об'єктом і оточуючі його тканини грудної залози дають стереотипну відповідь у вигляді розростання сполучнотканинної строми з формуванням капсули навколо імпланта та появи вогнищевих клітинних інфільтратів. Сучасні грудні імпланти, на відміну від імплантів попередніх десятиліть, за своєю структурою є більш досконалими, а рівень захисту від ушкоджень є набагато вищий. Ускладненням, пов'язаним з довготривалим використанням (до 20 років) імплантів, де в якості наповнювача використовували силікон низької якості або промисловий силікон, є проникнення низькомолекулярних частинок імпланта через його оболонку до оточуючих тканин з подальшим утворенням силіконових гранульом. У переважній більшості такі зміни розвиваються після механічної травматизації імпланта. Мета дослідження - встановити морфологічні критерії реакції тканин грудної залози після ушкоджень силіконового імпланта. Матеріалом для досліджень слугували гістологічні мікропрепарати тканин грудних залоз з архіву клініки "Grace Clinic" (м. Київ), за двостороннім погодженням з пацієнтками, що звернулися з метою повторної мамопластики. Тривалість перебування імплантів у грудній залозі становила від 6 до 20 років. Віковий діапазон жінок був у межах від 36 до 53 років. На препаратах, забарвлених гематоксиліном та еозином, були представлені біоптати тканин залоз 9-ох пацієнток з діагнозом деформації силіконових імплантів та порушенням цілісності їхньої стінки. Мікропрепарати візуалізували за допомогою світлового мікроскопа UlabXSP-137TLED при різних збільшеннях та фотографували камерою XCAM 1080P. Вивчення гістологічних препаратів м'яких тканин грудних залоз, з котрих були видалені силіконові імпланти, встановило зміни у стромально-клітинних елементах, а саме: оформлені волокнисті структури накопичувались у вигляді щільних капсул з елементами локальних контрактур; зі сторони клітинних елементів найбільш демонстративними були клітинні інфільтрати, у складі яких перебували макрофаги, лімфоцити та плазмоцити, що свідчило про високу ймовірність перебігу хронічного запального процесу. Практично в усіх досліджуваних зрізах були присутні велика кількість гігантських багатоядерних клітин сторонніх тіл, що свідчило про неможливість завершення макрофагами фагоцитозу з лізисом фагоцитованого матеріалу, котрий за своїм хімічним складом є силіконом імпланта. Усі описані явища можна трактувати як природну реакцію тканин на імплант, вміст котрого потрапив до м'яких тканин грудної залози. Таким чином, морфологічним критерієм реакції тканин грудної залози на пошкодження силіконового імпланта можна вважати наявність численних гігантських багатоядерних клітин сторонніх тіл, щільних капсул з елементами локальних контрактур та суттєвої переваги макрофагів, лімфоцитів та плазмоцитів у клітинних інфільтратах над іншими клітинними елементами.

Ключові слова: *молочна/грудна залоза, грудний імплант, пошкодження грудного силіконового імпланта, естетична хірургія, мікроскопія, гістопатологічна діагностика, імплант-асоційовані фіброзні зміни.*

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