

Breast Implant-Associated Tumors

Brustimplantatassoziierte Tumoren



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ABSTRACT

In addition to anaplastic large T-cell lymphomas (BIA-ALCL), other implant-related tumors have been described for some years. Squamous cell carcinoma (SSC) and B-cell lymphomas occurred in very rare cases. The unexplained pathogenesis as well as the unclear individual risk profile is an ongoing source of uncertainty for patients and physicians. The pathogenesis of the tumors is still largely not understood. While BIA-ALCL occurs more frequently with textured breast implants, other tumors were also observed with smooth implants and at other implant sites. Multiple potential mechanisms are discussed. It is suspected that the etiology of a chronic inflammatory response and subsequently immunostimulation is multifactorial and appears to play a key role in the malignant transformation. Since there are currently no sufficiently valid data for a specific risk assessment, this must be done with caution. This article presents the incidence, pathogenesis, as well as the level of evidence according to the current state of knowledge, and evaluates and discusses the current literature.

ZUSAMMENFASSUNG

Zusätzlich zu dem anaplastischen großzelligen T-Zell-Lymphom (BIA-ALCL) werden seit einigen Jahren weitere Tumoren im Zusammenhang mit Implantaten beschrieben. Sehr selten traten Plattenepithelkarzinome (SSC) und B-Zell-Lymphome auf. Die ungeklärte Pathogenese sowie das unklare individuelle Risikoprofil bringen eine anhaltende Verunsicherung von Patienten und Ärzten mit sich. Während das BIA-ALCL gehäuft im Zusammenhang mit texturierten Brustimplantaten auftritt, wurden die anderen Tumoren auch bei glattwandiger Textur und anderen Implantatlokalisationen beobachtet. Multiple potenzielle Mechanismen werden diskutiert. Eine vermutlich multifaktorielle Genese, die zu einer chronischen Entzündungsreaktion mit konsekutiver Immunstimulation führt, scheint eine Schlüsselrolle bei der malignen Transformation zu spielen. Für eine spezifische Risikobewertung liegen bisher keine ausreichend validen Daten vor, weshalb diese zurückhaltend erfolgen muss. Dargestellt werden Inzidenz, Pathogenese und Evidenzlevel des aktuellen Wissensstands sowie eine Bewertung und Diskussion der aktuellen Literatur.

Introduction

By far the most common tumor of these forms is breast implant-associated anaplastic large cell lymphoma (BIA-ALCL), a very rare subtype of non-Hodgkin's lymphoma. Unlike primary, sporadic ALCL of the breast, BIA-ALCL is not a tumor of the breast tissue. It occurs predominantly inside the implant capsule after textured silicone implants have been implanted.

It is difficult to assess the exact number of cases worldwide, as the unstructured reports are partly incomplete or redundant in various databases [1]. There is also often a lack of information on implant history, clinical course, and histology. In addition to unreliable data on incidence, there are also no reliable trade sales or implant data available. When comparing countries, there are significant differences between the reported cases, the reasons for which have not yet been clarified (cf. ► **Table 1**) [2].

Among the reported cases, there was a strikingly high number of macrotextured implants at the time of explantation. Despite unsatisfactory data, all macrotextured implants were removed from the market in April 2019. Microtextured implants are affected much less frequently; smooth implants, as far as we know, are not affected at all.

The passive vigilance systems currently in use are not sufficient to gain a better understanding of the disease, as well as to identify future implant-based problems early on. Instead, mandatory data collection with networking to evaluate all register data is required on an international level [3]. Germany is currently a global pioneer in this regard with the Implant Register Act [4].

Epidemiology of BIA-ALCL

Sporadic ALCL of the breast is a very rare disease with an incidence of approximately 0.037 per 1 million women. In addition, these are usually of B-cell origin. T-cell lymphomas affect less than 6% [5, 6]. By comparison, the occurrence of implant-associated ALCL is still very rare, but it is more common than would be expected in the sporadic forms [7, 8]. Retrospective studies on this are subject to limitations. This form has only been listed as a distinct entity since 2013. To date, both are difficult to distinguish, even by means of immunohistochemical or genetic analysis. Due to better discrimination techniques, the preliminary classification has been abandoned [9, 10, 11].

► **Table 1** Registered BIA-ALCL cases in the PROFILE database.

	Population (millions)	Cases	Deceased
Argentina	45.8	17	0
Australia	25.7	112	4
Austria	9	6	0
Belgium/Luxembourg	12.2	26	0
Brazil	214	31	1
Canada	28.3	38	1
Chile	19.6	2	0
China	1412	1	0
Denmark	5.9	13	0
France	67.7	99	4
Germany	84	46	0
Greece	10.6	1	0
Hungary	9.7	1	0
Israel	9.4	9	0
Italy	59.1	73	2
Japan	125.7	4	0
Mexico	126.7	14	0
Netherlands	17.5	70	2
New Zealand	5.1	20	1
Norway	5.4	13	0
Poland	37.7	10	0
Russia	144.7	8	0
Spain	47.6	74	3
Switzerland	8.7	11	0
Sweden	10.6	8	2
United Kingdom	67.5	78	1
United States	332	402	8
Other		60	2
Total		1233	31

Modified according to https://www.plasticsurgery.org/documents/Health-Policy/ALCL/PROFILE-Data-Summaries_Sept22.pdf
The cases recorded here do not correspond to the reports submitted to the FDA [1].

► **Table 2** Data on the surface texture of the cases reported to the FDA at the time of explantation [12].

Data on surface texture	n = 1130		
No data	295 (26%)		
Textured	798 (71%)		
Smooth	37 (3%)	Of which:	
		8	History of at least one textured implant
		10	Previous implant, no information about the surface
		18	No medical history
		1	One smooth implant and no known history of textured implant

The number of procedures with breast implants performed worldwide is unknown. According to conservative estimates, there are approximately 35 million breast implant patients. According to the global survey of the ISAPS (International Society of Aesthetic Plastic Surgery), approximately 1.68 million implant procedures are performed annually [12].

A total of 1130 cases were reported to the Food and Drug Administration (FDA) up to April 2022, including 59 deaths [13]. Canada has reported 64 confirmed cases and 25 suspected cases to date; of these, 3 were deaths (as of: 6 April 2022) [14]. Up to September 2022, Australian authorities received reports of 112 cases. In the EU, 398 cases were reported to the Task Force on BIA-ALCL, which consists of regulatory authorities; 345 of these cases could be confirmed [15]. In Germany, there is an obligation to report this disease. Currently, 46 BIA-ALCL cases have been registered with the Federal Institute of Drugs and Medical Devices (BfArM), with no deaths reported (update from 06.03.2023) [16].

Reports in the EU are very low compared to Australia and New Zealand. This is also reflected in the small number of epidemiological studies. Overall, data on the lifetime risk vary between 1.65 and 35 cases per 100 000 women with implants [5, 17, 18, 19, 20]. In estimating the number of implants required to induce BIA-ALCL, Cordeiro et al. reported 10 individual cases from a cohort of 3546 women. This corresponds to a cumulative incidence of 1 : 355 patients [19]. In contrast, Doren et al. assume an absolute cumulative risk of 29/1 million women up to 50 years of age and an increase to 82/1 million at 75 years of age. The estimated rate ranges from 1 : 6600 to 1 : 53300, depending on the implant type used [17]. For Australia and New Zealand, the risk is reported at 1 : 2832 for polyurethane, 1 : 3345 for biocell (BIOCELL, Allergan, Dublin, Ireland), and 1 : 86029 for siltex surfaces (Siltex, Mentor, Germany) [21].

Because no reliable trade sales or implant data are available, all authors took different approaches. For example, De Boer et al. extrapolated the prevalence of implants from 3000 randomly selected X-ray examinations and used this to determine the prevalence of female implant wearers in the Netherlands at 3.3%. The information on the implant types results from the manufacturer's information on the nationwide sales figures, but not on the products actually used [5].

Incomplete data on implant history also prevent a reliable evaluation. In most countries, textured implants are predominantly

used. It is therefore understandable why reports predominantly concern this type of surface. In contrast to this, almost exclusively smooth implants are used in the USA. Nevertheless, of the 1130 cases reported by the FDA, 798 had textured implants at the time of explantation, and only 37 had smooth surfaces (cf. ► **Table 2**).

Therefore, information on incidence, especially for evaluating specific implants, must be assessed with caution. Considering these data, a causal relationship with macrot textured implants must be assumed. Due to the lack of a reliable denominator, there has been no way to calculate the risk for other implant types. The available data indicate that patients with breast implants have a low absolute but high relative risk of developing BIA-ALCL.

However, in this context, it must be noted that the vast majority of diseases occurred with macrot textured implants. These implants have now been taken off the market, so a prospective risk assessment is almost impossible. Moreover, it is unclear whether we are only at the beginning of a problem due to the high rate of use of these products, and how surgeons should proceed with the capsule of this implant if revision procedures are required.

Causes

The pathogenesis of the tumor has not yet been clarified. Various hypotheses are being discussed that indicate a multifactorial etiology. In any case, immunostimulation by a subclinical chronic inflammatory response appears to play a relevant role. It is suspected that this persistent stimulation of T-cells triggers their deregulated clonal expansion. Triggers could be implant-related, i.e., an inflammatory response due to the implant sheath itself, abrasion of silicone particles or allergic hypersensitivity, but also procedure-related, e.g., bacterial contamination with certain pathogens and the formation of a biofilm. In addition, an altered immune response could play a role due to genetic characteristics of the patient [22, 23]. There is currently insufficient scientific evidence for any of these hypotheses.

It is also being discussed whether, at least in some cases, activated T lymphocytes are merely a lymphoproliferative reaction, as seen in other, mostly viral inflammatory processes, without necessarily resulting in malignant transformation. This would be a potential explanation for the relatively small number of ALCL cases requiring treatment in the past [15, 24, 25].

Implants

BIA-ALCL do not only occur with breast implants, but have also been described with orthopedic materials, dental implants, after bariatric procedures, and when liquid silicone fillers are used. However, this only affects a few individual cases, also with other types of lymphoma. Therefore, the causal relationship must be interpreted very cautiously at this time. In any case, none of these implants have an accumulation like we see with breast implants.

Implanted foreign bodies always trigger an inflammatory reaction and encapsulation. A complex wound healing cascade leads to leukocyte stimulation and differentiation. There is no knowledge to date as to which specific aspects, e.g., of a textured surface, change this course compared to other implant surfaces, and leads to malignant degeneration. However, it is postulated that textured implant surfaces may be more prone to a biofilm forming compared to smooth surfaces; in addition, the contact surface and area of continuous friction between the implant and the implant capsule, as well as the number of silicone particles released, are larger, which could increase the chronic inflammatory response [15, 26, 27, 28].

It is also unclear whether a different texture but equally “high” surface due to different manufacturing processes would have any effect. Examples include the salt-loss technique, in which salt crystals are washed off the surface during manufacturing, leaving sharply edged indentations. Gas diffusion at the time of vulcanization leads to a smaller depth and comparatively rounder pores, which are reduced again during imprint stamping. Finally, polyurethane foam is produced using an entirely different method. Yet many of these surfaces are classified in the same way.

Although it is not possible to conclusively assess the influence of the surface, the incidence varies considerably with different surfaces. Although implants are generally referred to as macro, micro, and nanotextured in comparison to smooth implants, there is currently no generally accepted classification. Therefore, surfaces may be assessed and presented differently by the manufacturers. Polyurethane surfaces are classified as macrot textured, but their foam-like structure makes it difficult to classify them with the given parameters. The most widely used is ISO 14607:2018, which classifies surfaces according to average roughness. This classification is merely descriptive and has not been clinically validated. Measurement technique and production deviations also limit the usefulness. The particular features mentioned above are also not addressed. There are currently approaches to integrate clinical aspects [12].

Focusing on the surface structure alone has not explained the different behaviors so far. Implants with the same surface classification should have a comparable incidence of BIA-ALCL.

Bacterial contamination

Despite the utmost care and efforts to maintain a sterile working environment, contamination with pathogens cannot always be avoided. Late contamination can occur by hematogenous pathways.

A working group in Australia found an increase of specific pathogens in the capsule of BIA-ALCL patients compared to benign capsule fibrosis. In addition, a higher number of pathogens

was detected [26]. The findings have not yet been confirmed by other groups [27]. The clinical relevance remains unclear; at any rate the influence of specific pathogens is now considered unlikely.

The colonization of the implant surface causes a biofilm to form. The subclinical inflammation caused by this could contribute to their malignant transformation due to the resulting chronic stimulation of T-cells over several steps and involving individual immunomodulatory factors [29]. Here, it is suspected that a higher surface relief may also contain a higher bacterial load and thus result in a higher risk for T-cell stimulation [30].

Abrasion of microparticles

The abrasion of silicone particles presumably affects implants with a rough surface in particular. This phenomenon has been known for some time; more recently, it has also been described in the context of the histological work-up of capsules affected by BIA-ALCL [4]. Again, it is suggested here that the immune system is activated through various pathways. A causal link to the formation of a tumor has not yet been established.

If implants are defective, the release of larger particles coincides with an inflammatory reaction to the foreign body, incl. by forming granulomas. Whether this is also the case for microparticles cannot be proven in the current literature. The macrophages activated by this process can express cytokines that stimulate a proliferation of T-cells. It is known that they are also transported to local lymph nodes [6]. The clinical relevance has not yet been clarified.

Genetic predisposition

A small number of BIA-ALCL reports occurred in patients with a known familial risk of breast carcinoma. The below-average time after implantation was striking [15, 31]. Some studies have also attempted to compare genetic alterations in the original breast tumor with those of BIA-ALCL or to find genetic abnormalities in tumor material in patients without prior breast carcinoma that may play a role in the pathogenesis. A mutation in genes that influence the activity of the JAK/STAT mechanism was found several times. This plays a role in the downregulation of immunological reactions. Thus, a disorder could be responsible for persistent immunostimulation [32]. Currently, genetic factors are considered to have a significant influence on the etiology [22].

Hypoxia

Tissue hypoxia is currently considered one of the most likely factors for the development of BIA-ALCL. During RNA sequencing, a dramatic upregulation of the hypoxia-associated biomarker carbonic anhydrase 9 (CA-9) has been shown in BIA-ALCL tissue compared to non-BIA ALCL tissue [33].

Clinical Presentation and Diagnosis

BIA-ALCL develop inside the implant sheath and can occur either in situ, i.e., limited to a seroma or as an adherent growth on the capsule, or can be infiltrative. In most cases, a large seroma containing tumor cells develops in a short period of time. This occurs

at least one year after implantation, on average after 7 to 10 years, with reconstructive and esthetic implants being affected with relatively equal frequency. Smaller seromas around an implant are often seen and do not require further diagnosis if the clinical presentation and imaging are otherwise unremarkable. Approximately 8–24% of patients have an isolated or concomitant solid tumor. Systemic symptoms, such as a rash and fever, are very rare. The infiltrative stages may show lymph node involvement, regardless of whether a solid tumor is present [34].

Further diagnostics are performed by ultrasound. Sensitivity and specificity for detecting effusions are reported as 84% and 75% respectively, and 46% and 100% respectively for solid tumors [35]. An ultrasound is therefore the appropriate method, especially for screening. According to the consensus guideline, the efferent lymphatic pathways should be examined for suspicious changes in addition to fluid retention or a mass lesion. If there is any ambiguity, nuclear magnetic resonance (NMR) is recommended. CT examinations play a minor role. A PET-CT is recommended for questions about systemic spread [36, 37].

A diagnosis is made by analyzing the seroma. Here, it is important to obtain sufficient cell material for flow cytometry. At least 50 ml are required. Serial punctures should be avoided as the diluting effect makes diagnosis more difficult. In addition, a bacterial examination should be performed [38]. Solid tumors are biopsied.

If cell morphology shows abnormalities, the immunohistochemistry panel is expanded. This is also done to exclude other malignant or benign processes that may have a similar picture to BIA-ALCL. CD30 and ALK are the most well-known markers, the former being consistently positive and the latter always negative. However, when considered in isolation, they are not conclusive of BIA-ALCL. Other cutaneous or systemic forms of ALCL may also be ALK-negative. CD30 is a nonspecific marker that can also be found on benign activated T- and B-cells, e.g., in connection with viral infections. Even sparse CD30-positive lymphocytes with unremarkable morphology do not require further diagnostic confirmation. The markers must be detected in cells that exhibit the typical cytological properties of an ALCL. Therefore, other markers must also be included, where appropriate [30, 39, 40].

Assessing whether capsular infiltration is present is essential for further treatment and prognosis. After complete en-bloc resection of the capsule, at least 12 biopsies are recommended for this purpose to assess the resection margins [41].

Treatment of BIA-ALCL

There are guidelines and recommendations for treatment [34]. Complete surgical resection of the tumor including the implant capsule (en-bloc resection) is the primary treatment and is crucial for prognosis. In the event of incomplete resection or systemic involvement, adjuvant therapy may be required. This has so far been largely based on the treatment of systemic ALCL as there is a lack of disease-specific experience.

Removal of the sentinel lymph node is not recommended; an excisional biopsy should be performed if lymph nodes are abnormal. In up to 4.6% of cases, the tumor occurred bilaterally. It is therefore recommended to also remove a contralateral implant. Immediate reconstruction with a smooth implant is discussed, as

well as primary or secondary reconstruction using the patient's own tissue. To date, there are no standardized, internationally agreed recommendations for this or for follow-up care [34].

Prognosis

BIA-ALCL have a very favorable prognosis if detected early on and treated consistently. According to current knowledge, in-situ tumors are treated curatively by capsule resection alone. Spontaneous regression has been described in individual cases [24]. The problem here is that there are still no parameters to identify benign courses [42]. Infiltrative stages that cannot be fully treated with surgery have a less favorable prognosis with a mortality of up to 40% in 2 years [5, 15].

Other Breast Implant-Associated Tumors

Viral infections are responsible for 15%–20% of all human tumors [43]. The Epstein-Barr Virus (EBV) also causes B-cell lymphoma, Burkitt lymphoma, and diffuse large B-cell lymphoma. It has also long been known that chronic inflammation can lead to malignant transformation and squamous cell carcinoma. Marjolin's ulcers develop from inflammation and ulcers on the leg.

In recent years, in addition to BIA-ALCL, implant-associated diffuse large B-cell lymphomas (DLBCL) have also been described, such as breast implant-associated EBV-positive diffuse large B-cell lymphoma [44, 45, 46, 47]. These are usually negative for ALK, CD2, CD3, and B-cell markers [48], but positive for CD20 [44, 47, 48, 49], CD5, BCL-2, CD21, CD23, IgD, IgM, [49]. EBV-positive diffuse large B-cell lymphomas are positive for CD20, CD30, CD79a, MUM1, and PAX-5 [44, 47, 48], and, similar to BIA-ALCL, are associated in most cases with textured implants [45, 47]. In one case, DLBCL was described after implantation of a smooth implant [50]. The prosthesis was often implanted well over 10 years prior [44, 45, 47, 48]. The FDA has documented fewer than 30 cases based on literature searches; 12 cases have been reported to date (as of: 8 September 2022) [51].

Similar to BIA-ALCL, chronic inflammation is also thought to play a major role in the pathogenesis of DLBCL [52].

However, Bacon and O'Donoghue argue that in some of the supposedly implant-associated lymphomas described [53, 54], a causal relationship between lymphoma and implant is unlikely, especially if it was found only very close to the implant [53] or on the abluminal surface [54] of the implant capsule [55]. In addition, some patients also had a systemic lymphoma. In contrast, they see a potential correlation with DLBCL (DLBCL-CI) which is associated with chronic inflammation, or fibrin-associated DLBCL (FA-DLBCL) [55].

Since DLBCL-CI/FA-DLBCL are associated with symptoms similar to BIA-ALCL and can therefore also be excluded in the presence of CD-30-positive large cell lymphoma [48], these diseases should also be excluded in the presence of late seroma. If suspected, EBV (EBV-encoded RNA) should be included in the immunohistochemical panel.

In terms of treatment, there is still no global consensus due to the rarity, but prompt en-bloc resection, as for BIA-ALCL [36], is recommended [49, 56]. As in cases of suspected BIA-ALCL, a

puncture and cytological examination of the markers mentioned above should also be performed in cases of periprosthetic seroma that occurred later than 6 months after surgery [49, 50].

Breast implant-associated squamous cell carcinoma (BIA-SCC)

Breast implant-associated squamous cell carcinoma (SCC) was described as early as 1994 [57]. To date, the FDA has documented 19 cases based on literature searches (as of: 8 March 2023) [51]. This extremely rare disease is associated with both textured and smooth implants [51, 58, 59, 60, 61]. A case of SCC following the injection of liquid silicone into the breast has also been documented [62]. Most cases describe the first prosthesis being implanted more than 10 years prior [57, 59, 60, 61, 63, 64, 65].

The origin of a squamous epithelium is unclear. Metaplasia of the capsule cells due to a chronic inflammatory stimulus is possible. However, abrasion implantation in the context of implant insertion or laceration of the gland ducts is also being discussed [57].

Similar to BIA-ALCL, implant-associated SCC is also associated with a late seroma; however, histopathologically, compared to BIA-ALCL, there is usually a circumscribed tumor in addition to the periprosthetic seroma [57, 58, 64]. Antibodies against cytokeratin should be included during the work-up.

Due to the very rare cases described to date, there is still no clear consensus on treatment. However, it is a highly aggressive tumor with rapid infiltration beyond the capsule, as well as poor prognosis. Rapid and radical treatment is therefore essential. Again, an en-bloc or R0 resection is recommended, which in some cases has been supplemented by adjuvant radiotherapy or radiochemotherapy [61, 64, 66]. Rapid progression with metastasis was described in three cases despite R0 resection with adjuvant radiotherapy or radiochemotherapy [61, 64]; in several cases, no follow-up information was provided [57, 60]. Only Palletta et al. described no local or systemic regression after one year of follow-up [65].

Conclusion

Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is a rare complication that predominantly occurs with macrotextured breast implants. The pathogenesis is still largely unknown. Several theories with different approaches are being discussed, so there may be multiple factors at play. In all hypotheses, however, a chronic inflammatory response is the driving force.

Prognosis is very favorable if treatment is started early. However, since more advanced stages have a significantly less favorable course, a comprehensive preoperative risk assessment and patient information prior to implant insertion is essential, as well as ongoing follow-up care. The other tumors described in the context of breast implants are extremely rare. However, SCC has a much poorer prognosis and must be detected early and treated radically. The prophylactic removal of implants that are unremarkable both clinically and in imaging is not recommended.

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Conflict of Interest

The authors declare that they have no conflict of interest.

References/Literatur

- [1] ASPS. PROFILE Registry and FDA BIA-ALCL Data Comparison. Accessed May 17, 2023 at: <https://www.plasticsurgery.org/documents/Health-Policy/ALCL/PROFILE-Data-Summaries.pdf>
- [2] Groth AK, Clemens MW, Graf R et al. Breast Implant-Associated Anaplastic Large-Cell Lymphoma in Brazil: What Are We Missing? *Plast Reconstr Surg* 2022; 150: 970e–978e. doi:10.1097/prs.0000000000009652
- [3] Spronk PER, Begum H, Vishwanath S et al. Toward International Harmonization of Breast Implant Registries: International Collaboration of Breast Registry Activities Global Common Data Set. *Plast Reconstr Surg* 2020; 146: 255–267. doi:10.1097/PRS.00000000000006969
- [4] Prantl L, von Fritschen U, Liebau J et al. Concept for a National Implant Registry to Improve Patient Safety. *Handchir Mikrochir Plast Chir* 2016; 48: 320–329. doi:10.1055/s-0042-118863
- [5] de Boer M, van Leeuwen FE, Hauptmann M et al. Breast Implants and the Risk of Anaplastic Large-Cell Lymphoma in the Breast. *JAMA Oncol* 2018; 4: 335–341. doi:10.1001/jamaoncol.2017.4510
- [6] Fleury EF C. Silicone Induced Granuloma of Breast Implant Capsule (SIGBIC) diagnosis: Breast Magnetic Resonance (BMR) sensitivity to detect silicone bleeding. *PLoS One* 2020; 15: e0235050. doi:10.1371/journal.pone.0235050
- [7] Ramos-Gallardo G, Carballo-Zarate AA, Cuenca-Pardo J et al. What is the Evidence of Lymphoma in Patients with Prostheses Other Than Breast Implants? *Aesthetic Plast Surg* 2020; 44: 286–294. doi:10.1007/s00266-019-01569-1
- [8] von Fritschen U, Solbach C, Prantl L. Wie sicher sind Silikonimplantate? *Senologie* 2019; 16: 92–93. doi:10.1055/a-0897-0043
- [9] Blombery P, Thompson ER, Prince HM. Molecular Drivers of Breast Implant-Associated Anaplastic Large Cell Lymphoma. *Plast Reconstr Surg* 2019; 143: 59S–64S. doi:10.1097/PRS.0000000000005570
- [10] Stuttgen K, Croessmann S, Fetting J et al. Pathogenic Germline Variants in Patients With Metastatic Breast Cancer. *JAMA Oncol* 2019; 5: 1506–1508. doi:10.1001/jamaoncol.2019.3116
- [11] Swerdlow SH, Campo E, Pileri SA et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood* 2016; 127: 2375–2390. doi:10.1182/blood-2016-01-643569
- [12] ISAPS. International Survey on Aesthetic/Cosmetic Procedures. Accessed March 02, 2023 at: https://www.isaps.org/media/vdpdanke/isaps-global-survey_2021.pdf
- [13] FDA. Medical Device Reports of Breast Implant-Associated Anaplastic Large Cell Lymphoma. Accessed February 02, 2023 at: <https://www.fda.gov/medical-devices/breast-implants/medical-device-reports-breast-implant-associated-anaplastic-large-cell-lymphoma>

- [14] Government of Canada. Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) – Canadian Surveillance 2021 Data. Accessed February 02, 2023 at: <https://health-infobase.canada.ca/datalab/bia-alcl-blog.html>
- [15] European Commission Scientific Committee on Health, Environmental and Emerging Risks (SCHEER). Final Opinion on the safety of breast implants in relation to anaplastic large cell lymphoma. Accessed February 02, 2023 at: https://health.ec.europa.eu/system/files/2022-08/scheer_o_018.pdf
- [16] BfArM. Möglicher Zusammenhang zwischen Brustimplantaten und der Entstehung eines anaplastischen großzelligen Lymphoms (ALCL). Accessed February 02, 2023 at: https://www.bfarm.de/SharedDocs/Risikoinformationen/Medizinprodukte/DE/Brustimplantate_ALCL_FDA.html;jsessionid=E76572DA3D2363EFCB0DCD330F94E0A3.intranet662?nn=939498
- [17] Doren EL, Miranda RN, Selber JC et al. U.S. Epidemiology of Breast Implant-Associated Anaplastic Large Cell Lymphoma. *Plast Reconstr Surg* 2017; 139: 1042–1050. doi:10.1097/prs.0000000000003282
- [18] Loch-Wilkinson A, Beath KJ, Magnusson MR et al. Breast Implant-Associated Anaplastic Large Cell Lymphoma in Australia: A Longitudinal Study of Implant and Other Related Risk Factors. *Aesthet Surg J* 2020; 40: 838–846. doi:10.1093/asj/sjz333
- [19] Cordeiro PG, Ghione P, Ni A et al. Risk of breast implant associated anaplastic large cell lymphoma (BIA-ALCL) in a cohort of 3546 women prospectively followed long term after reconstruction with textured breast implants. *J Plast Reconstr Aesthet Surg* 2020; 73: 841–846. doi:10.1016/j.bjps.2019.11.064
- [20] Wang Y, Zhang Q, Tan Y et al. Current Progress in Breast Implant-Associated Anaplastic Large Cell Lymphoma. *Front Oncol* 2021; 11: 785887. doi:10.3389/fonc.2021.785887
- [21] Magnusson M, Beath K, Cooter R et al. The Epidemiology of Breast Implant-Associated Anaplastic Large Cell Lymphoma in Australia and New Zealand Confirms the Highest Risk for Grade 4 Surface Breast Implants. *Plast Reconstr Surg* 2019; 143: 1285–1292. doi:10.1097/PRS.00000000000005500
- [22] de Boer M, Hauptmann M, Hijmering NJ et al. Increased prevalence of BRCA1/2 mutations in women with macrotextured breast implants and anaplastic large cell lymphoma of the breast. *Blood* 2020; 136: 1368–1372. doi:10.1182/blood.2019004498
- [23] DeCoster RC, Clemens MW, Di Napoli A et al. Cellular and Molecular Mechanisms of Breast Implant-Associated Anaplastic Large Cell Lymphoma. *Plast Reconstr Surg* 2021; 147: 30e–41e. doi:10.1097/prs.00000000000007423
- [24] Fleming D, Stone J, Tansley P. Spontaneous Regression and Resolution of Breast Implant-Associated Anaplastic Large Cell Lymphoma: Implications for Research, Diagnosis and Clinical Management. *Aesthetic Plast Surg* 2020; 44: 1109–1115. doi:10.1007/s00266-020-01810-2
- [25] Loch-Wilkinson A, Beath KJ, Knight RJW et al. Breast Implant-Associated Anaplastic Large Cell Lymphoma in Australia and New Zealand: High-Surface-Area Textured Implants Are Associated with Increased Risk. *Plast Reconstr Surg* 2017; 140: 645–654. doi:10.1097/PRS.00000000000003654
- [26] Hu H, Johani K, Almatroudi A et al. Bacterial Biofilm Infection Detected in Breast Implant-Associated Anaplastic Large-Cell Lymphoma. *Plast Reconstr Surg* 2016; 137: 1659–1669. doi:10.1097/PRS.00000000000002010
- [27] Walker JN, Hanson BM, Pinkner CL et al. Insights into the Microbiome of Breast Implants and Periprosthetic Tissue in Breast Implant-Associated Anaplastic Large Cell Lymphoma. *Sci Rep* 2019; 9: 10393. doi:10.1038/s41598-019-46535-8
- [28] Munhoz AM, Clemens MW, Nahabedian MY. Breast Implant Surfaces and Their Impact on Current Practices: Where We Are Now and Where Are We Going? *Plast Reconstr Surg Glob Open* 2019; 7: e2466. doi:10.1097/GOX.00000000000002466
- [29] Malcolm TI, Hodson DJ, Macintyre EA et al. Challenging perspectives on the cellular origins of lymphoma. *Open Biol* 2016; 6: 160232. doi:10.1098/rsob.160232
- [30] Jones P, Mempin M, Hu H et al. The Functional Influence of Breast Implant Outer Shell Morphology on Bacterial Attachment and Growth. *Plast Reconstr Surg* 2018; 142: 837–849. doi:10.1097/PRS.00000000000004801
- [31] Adlard J, Burton C, Turton P. Increasing Evidence for the Association of Breast Implant-Associated Anaplastic Large Cell Lymphoma and Li Fraumeni Syndrome. *Case Rep Genet* 2019; 2019: 5647940. doi:10.1155/2019/5647940
- [32] Laurent C, Nicolae A, Laurent C et al. Gene alterations in epigenetic modifiers and JAK-STAT signaling are frequent in breast implant-associated ALCL. *Blood* 2020; 135: 360–370. doi:10.1182/blood.2019001904
- [33] Oishi N, Hundal T, Phillips JL et al. Molecular profiling reveals a hypoxia signature in breast implant-associated anaplastic large cell lymphoma. *Haematologica* 2021; 106: 1714–1724. doi:10.3324/haematol.2019.245860
- [34] Clemens MW, Jacobsen ED, Horwitz SM. 2019 NCCN Consensus Guidelines on the Diagnosis and Treatment of Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL). *Aesthet Surg J* 2019; 39: S3–S13. doi:10.1093/asj/sjy331
- [35] Adrada BE, Miranda RN, Rauch GM et al. Breast implant-associated anaplastic large cell lymphoma: sensitivity, specificity, and findings of imaging studies in 44 patients. *Breast Cancer Res Treat* 2014; 147: 1–14. doi:10.1007/s10549-014-3034-3
- [36] Clemens MW, Horwitz SM. NCCN Consensus Guidelines for the Diagnosis and Management of Breast Implant-Associated Anaplastic Large Cell Lymphoma. *Aesthet Surg J* 2017; 37: 285–289. doi:10.1093/asj/sjw259
- [37] Clemens MW, DeCoster RC, Fairchild B et al. Finding Consensus After Two Decades of Breast Implant-Associated Anaplastic Large Cell Lymphoma. *Semin Plast Surg* 2019; 33: 270–278. doi:10.1055/s-0039-1696998
- [38] Fricke A, Wagner JA, Kricheldorf J et al. Microbial detection in seroma fluid preceding the diagnosis of breast implant-associated anaplastic large cell lymphoma: a case report and review of the literature. *Case Reports Plast Surg Hand Surg* 2019; 6: 116–120. doi:10.1080/23320885.2019.1593846
- [39] DePaola NEK, Coggins H. Breast Implant-Associated Anaplastic Large Cell Lymphoma: What We Know. *J Adv Pract Oncol* 2019; 10: 54–61
- [40] Quesada AE, Medeiros LJ, Clemens MW et al. Breast implant-associated anaplastic large cell lymphoma: a review. *Mod Pathol* 2019; 32: 166–188. doi:10.1038/s41379-018-0134-3
- [41] Lyapichev KA, Piña-Oviedo S, Medeiros LJ et al. A proposal for pathologic processing of breast implant capsules in patients with suspected breast implant anaplastic large cell lymphoma. *Mod Pathol* 2020; 33: 367–379. doi:10.1038/s41379-019-0337-2
- [42] Magnusson MR, Deva AK. Letter to Editor: Fleming D, Stone J, Tansley P. Spontaneous Regression and Resolution of Breast Implant-Associated Anaplastic Large Cell Lymphoma: Implications for Research, Diagnosis and Clinical Management, APS 2018. *Aesthetic Plast Surg* 2018; 42: 1164–1166. doi:10.1007/s00266-018-1141-y
- [43] Schiller JT, Lowy DR. An Introduction to Virus Infections and Human Cancer. *Recent Results Cancer Res* 2021; 217: 1–11. doi:10.1007/978-3-03-57362-1_1
- [44] Khoo C, McTigue C, Hunter-Smith DJ et al. EBV positive fibrin/chronic inflammation associated diffuse large B-cell lymphoma: an incidental finding associated with a breast implant. *Pathology* 2021; 53: 673–675. doi:10.1016/j.pathol.2020.09.022
- [45] Malata CM, Madada-Nyakauru RN, Follows G et al. Epstein-Barr Virus-associated Diffuse Large B-cell Lymphoma Identified in a Breast Implant Capsule: A New Breast Implant-Associated Lymphoma? *Ann Plast Surg* 2021; 86: 383–386. doi:10.1097/SAP.00000000000002537

- [46] Medeiros LJ, Marques-Piubelli ML, Sangiorgio VFI et al. Epstein-Barr-virus-positive large B-cell lymphoma associated with breast implants: an analysis of eight patients suggesting a possible pathogenetic relationship. *Mod Pathol* 2021; 34: 2154–2167. doi:10.1038/s41379-021-00863-1
- [47] Morgan S, Tremblay-LeMay R, Lipa JE et al. Breast implant-associated EBV-positive diffuse large B-cell lymphoma: Two case reports and literature review. *Pathol Res Pract* 2021; 226: 153589. doi:10.1016/j.prp.2021.153589
- [48] Mansy M, Wotherspoon AC, El-Sharkawi D et al. Fibrin-associated diffuse large B-cell lymphoma misdiagnosed as breast implant-associated anaplastic large-cell lymphoma. *Histopathology* 2021; 79: 269–271. doi:10.1111/his.14372
- [49] Chen VW, Hoang D, Clancy S. Breast Implant-Associated Bilateral B-Cell Lymphoma. *Aesthet Surg J* 2020; 40: NP52–NP58. doi:10.1093/asj/sjy093
- [50] Smith BK, Gray SS. Large B-cell lymphoma occurring in a breast implant capsule. *Plast Reconstr Surg* 2014; 134: 670e–671e. doi:10.1097/PRS.0000000000000535
- [51] FDA. Breast Implants: Reports of Squamous Cell Carcinoma and Various Lymphomas in Capsule Around Implants. Accessed February 02, 2023 at: <https://www.fda.gov/medical-devices/safety-communications/breast-implants-reports-squamous-cell-carcinoma-and-various-lymphomas-capsule-around-implants-fda>
- [52] Copie-Bergman C, Niedobitek G, Mangham DC et al. Epstein-Barr virus in B-cell lymphomas associated with chronic suppurative inflammation. *J Pathol* 1997; 183: 287–292. doi:10.1002/(SICI)1096-9896(199711)183:3287::AID-PATH9323.0.CO;2-Q
- [53] Ryan C, Ged Y, Quinn F et al. Classical Hodgkin Lymphoma Arising Adjacent to a Breast Implant. *Int J Surg Pathol* 2016; 24: 448–455. doi:10.1177/1066896916632587
- [54] Har-Shai L, Har-Shai Y, Metanes I et al. Composite breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) and extra-nodal marginal zone lymphoma (MZL) in the capsule of a silicone breast implant. *Autoimmun Rev* 2019; 18: 556–557. doi:10.1016/j.autrev.2019.03.014
- [55] Bacon CM, O'Donoghue JM. Commentary on: Breast Implant-Associated Bilateral B-Cell Lymphoma. *Aesthet Surg J* 2020; 40: NP59–NP62. doi:10.1093/asj/sjz304
- [56] Vorstenbosch J, Chu JJ, Ariyan CE et al. Clinical Implications and Management of Non-BIA-ALCL Breast Implant Capsular Pathology. *Plast Reconstr Surg* 2023; 151: 20e–30e. doi:10.1097/PRS.00000000000009780
- [57] Kitchen SB, Paletta CE, Shehadi SI et al. Epithelialization of the lining of a breast implant capsule. Possible origins of squamous cell carcinoma associated with a breast implant capsule. *Cancer* 1994; 73: 1449–1452. doi:10.1002/1097-0142(19940301)73:51449::aid-cnrcr28207305203.0.co;2-j
- [58] Soni SE, Laun JC, Beard AS et al. Breast Implant Capsule-Associated Squamous Cell Carcinoma during Pregnancy: A Mimicker of Breast Implant-Associated Anaplastic Large-Cell Lymphoma. *Plast Reconstr Surg* 2022; 150: 926e–928e. doi:10.1097/PRS.00000000000009506
- [59] Buchanan PJ, Chopra VK, Walker KL et al. Primary Squamous Cell Carcinoma Arising From a Breast Implant Capsule: A Case Report and Review of the Literature. *Aesthet Surg J* 2018. doi:10.1093/asj/sjy092
- [60] Zomerlei TA, Samarghandi A, Terando AM. Primary Squamous Cell Carcinoma Arising from a Breast Implant Capsule. *Plast Reconstr Surg Glob Open* 2015; 3: e586. doi:10.1097/GOX.0000000000000567
- [61] Olsen DL, Keeney GL, Chen B et al. Breast implant capsule-associated squamous cell carcinoma: a report of 2 cases. *Hum Pathol* 2017; 67: 94–100. doi:10.1016/j.humpath.2017.07.011
- [62] Smith LF, Smith TT, Yeary E et al. Squamous cell carcinoma of the breast following silicone injection of the breasts. *J Okla State Med Assoc* 1999; 92: 126–130
- [63] Goldberg MT, Llaneras J, Willson TD et al. Squamous Cell Carcinoma Arising in Breast Implant Capsules. *Ann Plast Surg* 2021; 86: 268–272. doi:10.1097/SAP.0000000000002524
- [64] Zhou YM, Chaudhry HE, Shah A et al. Breast Squamous Cell Carcinoma Following Breast Augmentation. *Cureus* 2018; 10: e3405. doi:10.7759/cureus.3405
- [65] Paletta C, Paletta FX jr., Paletta FX sr.. Squamous cell carcinoma following breast augmentation. *Ann Plast Surg* 1992; 29: 425–429. doi:10.1097/0000637-199211000-00009
- [66] Whaley RD, Aldrees R, Dougherty RE et al. Breast Implant Capsule-Associated Squamous Cell Carcinoma: Report of 2 Patients. *Int J Surg Pathol* 2022; 30: 900–907. doi:10.1177/10668969221086940