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"Breast Implant - Associated Anaplastic Large Cell Lymphoma (BIA- ALCL)" – Etiopatogenese

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“Breast Implant - Associated Anaplastic Large Cell Lymphoma (BIA- ALCL)” – Etiopatogenese / Breast Implant Associated Anaplastic Large Cell Lymphoma (BIA- ALCL) – Etiopathogenesis

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TÍTULO ~~DISSERTAÇÃO~~/MONOGRAFIA (riscar o que não interessa)

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Dedicatória

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Monografia

Title page

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Short title: Etiopathogenesis of BIA- ALCL

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ÍNDICE

Resumo:

Introdução: o linfoma anaplásico de grandes células associado a próteses mamárias (BIA-ALCL) é um linfoma não Hodgkin de células T, negativo para a cínase de linfomas anaplásicos (ALK-), tendo sido descrito inicialmente por Keech Jr em 1997 e reconhecido como uma nova doença em 2017 pela Organização Mundial da Saúde. Existem principalmente três principais fatores que levam ao desenvolvimento de BIA-ALCL, relacionados com a predisposição genética, contaminação bacteriana e inflamação crónica. Todos os casos devidamente relatados foram descritos em contexto de utilização de implantes mamários texturizados, o que levou a comunidade científica a especular sobre a correlação destes com a sua etiopatogénese. Neste estudo, pretendemos examinar a literatura existente sobre a etiopatogénese do BIA-ALCL e explorar alguns mecanismos de forma a selecionar o melhor tipo de implante e procedimentos para reduzir a morbilidade associada à dessa doença.

Materiais e Métodos: foi efetuada uma pesquisa na base de dados na plataforma (PubMed) através dos termos, ("breast implant-associated anaplastic large cell lymphoma" OR "BIA-ALCL") AND ("etiopathogenesis" OR "pathogenesis" OR "etiology") tendo sido selecionados os artigos publicados entre 2013 e 2023.

Resultados: o BIA-ALCL tem diversas etiologias propostas. Nesta revisão da literatura foi possível explorar cada uma das mesmas, escrutinando a correlação entre o processo de inflamação crónica e de que forma este está relacionado com o desenvolvimento do BIA-ALCL, quer seja pela reação provocada pela superfície macro texturada da prótese, quer seja pela presença de um biofilme mais extenso com maior prevalência da bactéria

Ralstonia spp.. Ainda relativamente à proliferação bacteriana, esta tem uma correlação linear com a texturização do implante utilizado, desencadeando um processo de inflamação crónica adjuvado pela desregulação do sistema JAK/STAT3, devido a mutações genéticas nas proteínas JAK1 e STAT3, predispondo ao desenvolvimento de células T CD30+/ALK- percursoras do BIA-ALCL. Juntamente com estas, mutações BRCA1/2, TP53 estão associados a uma maior prevalência deste outcome.

Discussão: as diversas teorias sobre a etiopatogenese do BIA-ALCL, apesar de diferentes, convergem até certo ponto no que concerne à existência de um processo de inflamação crónica que poderá ser percursor, em indivíduos geneticamente suscetíveis, do desenvolvimento do BIA-ALCL. Por se tratar de uma patologia recente e de desenvolvimento tardio, ainda não existe um consenso, sendo por este motivo necessários estudos futuros.

Conclusão: atualmente, a interação entre a texturização do implante, o biofilme, a inflamação crónica e os fatores genéticos é a teoria mais plausível e aceita pela comunidade científica e profissionais de saúde, onde estes diferentes mecanismos são capazes de promover o desenvolvimento do BIA-ALCL. O BIA-ALCL é uma entidade relativamente recente, com um desenvolvimento indolente, e a utilização de plataformas de registo de dados é importante para o estudo dessa patologia. São necessários, ainda assim, futuros estudos para melhor compreender a correlação entre os diferentes fatores e inferir com exatidão sobre a etiologia do BIA-ALCL.

ABSTRACT:

Introduction: BIA-ALCL is a non-Hodgkin's T cell lymphoma and anaplastic lymphoma Kinase negative (ALK-) firstly described by Keech Jr in 1997 and recognised as a new disease in 2016 by World Health Organization. There are above all three major factors leading to the development of BIA-ALCL laying on genetic background, bacterial contamination and chronic inflammation. Most of the cases have been reported in the context of textured breast implants, which can lead the scientific community to speculate about the etiphatogenesis. Herein, we intend to scrutinize the existing literature about BIA-ALCL etiopathogenesis and explore some mechanisms to choose the best type of implant and procedures to reduce this disease morbidity.

Material and Methods: A literature review was conducted in "PubMed" database using the following query: ("breast implant-associated anaplastic large cell lymphoma" OR "BIA-ALCL") AND ("etiopathogenesis" OR "pathogenesis" OR "etiology"). The articles published between 2013 and 2023 were selected.

Results: BIA-ALCL has various proposed etiologies, and in this literature review, it was possible to explore each of them, scrutinizing the correlation between the process of chronic inflammation and how it is related to the development of BIA-ALCL, whether through the reaction caused by the macro-textured surface of the implant or the presence of a more extensive biofilm with a higher prevalence of Ralstonia spp. bacteria. Regarding bacterial proliferation, there is a linear correlation with the texturing of the used implant, triggering a chronic inflammation process aided by dysregulation of the JAK/STAT3 pathway due to genetic mutations in JAK1 and STAT3 proteins,

predisposing the development of T CD30+/ALK- cells precursors of BIA-ALCL. Along with these, mutations in BRCA1/2, TP53 are also associated with a higher prevalence of this outcome.

Discussion: The various theories on the etiopathogenesis of BIA-ALCL, although different, converge to some extent regarding the existence of a chronic inflammatory process that may precede the development of BIA-ALCL. As it is a recent and indolent course pathology, there is currently no consensus, making further studies necessary.

Conclusion: Currently, the interaction between implant texturing, biofilm, chronic inflammation and genetic drive is the most plausible and accepted theory by the scientific community and healthcare professionals where these different mechanisms are capable of promoting the development of BIA-ALCL. BIA-ALCL is a relatively recent entity with an indolent development, and the use of data registry platforms is important for the study of this pathology. Future studies are still needed to better understand the correlation between these different factors and accurately infer the etiology of BIA-ALCL.

Keywords: BIA-ALCL, Breast Implant - associated Anaplastic Large Cell Lymphoma, etiopathogenesis, pathogenesis, etiology.

1. Introduction

Breast implant use has been linked to an uncommon non-lymphoma Hodgkin's called breast implant-associated anaplastic large cell lymphoma (BIA-ALCL). Since the illness was initially identified in 1997, more than 1300 cases have been recorded globally. This type of anaplastic lymphoma kinase (ALK)-negative T cells tend to assemble inside the fibrous capsule that encloses the breast implant [1, 2, 30].

Although the precise cause of BIA-ALCL is still unknown, it is believed to be linked to persistent inflammation brought on by the presence of the breast implant. [1] Host's inflammatory chronic response to the implant shell or bacterial colonization of the implant surface could both cause inflammation. Moreover, it is thought that BIA-ALCL development may be influenced by hereditary factors [4].

BIA-ALCL often manifests after several months to many years, being detected on average 8-10 years after implantation with a delayed onset of symptoms. The most typical clinical symptom is a late-onset seroma (fluid accumulation) surrounding the breast implant, which is frequently accompanied by discomfort, swelling, or a palpable mass. Breast asymmetry, capsular contracture, and skin rash are among other less frequent manifestations [11, 4].

A combination of clinical and laboratory results, such as seroma fluid analysis, imaging tests, and histological analysis of tissue specimens, are used to make the diagnosis of BIA-ALCL. Finding ALK-negative T cells inside the fibrous capsule that surrounds the breast implant is the gold standard for diagnosis [4, 14, 41].

The surgical removal of the breast implant and surrounding capsule is mandatory when the diagnosis of BIA-ALCL is confirmed (total capsulectomy). Chemotherapy and radiation therapy may be needed in cases when the disease has progressed outside the

breast capsule, which is not a common development of the disease. Two thirds of the patients with BIA-ALCL have a fair prognosis, with a reported five-year survival rate of 89% [41].

In sum, the usage of breast implants has been linked to BIA-ALCL, an uncommon form of T cell lymphoma. Whilst the exact cause of the condition is unknown, persistent inflammation brought on by the implant is likely to be a contributing factor [14].

It is crucial to comprehend the etiopathogeny, or underlying causes and mechanisms, of BIA-ALCL once early detection, diagnosis, definition of risk groups and efficient management of the disease can all be aided by acquiring a thorough grasp of the etiopathogeny of BIA-ALCL. Healthcare workers can increase their capacity to spot BIA-ALCL early on by learning the elements that contribute to the disease's development. This will enable specific prevention on specific risk groups, prompt intervention and better patient outcomes. Additionally, a deeper comprehension of the etiopathogeny can help in the development of certain diagnostic tests that enable the precise and effective detection of BIA-ALCL.

In summary, understanding the etiopathogeny of BIA-ALCL is essential for lymphoma research progress, early detection, correct diagnosis, efficient therapy, identification of risk factors, and creation of preventative methods. We can significantly advance patient outcomes and advance the general safety of breast implant surgeries by examining the fundamental causes and processes of BIA-ALCL

In this review, we aim to explore and synthetize the latest findings on the aetiology of the BIA-ALCL and resume the current existent theories. We further discuss the most accepted theory and briefly discuss the disease presentation, diagnosis and therapeutics.

2. Material and Methods

In this review, we overview the current literature related to the etipathogenesis of BIA-ALCL. A literature search was performed in the PubMed database, using the following searching terms, ("breast implant-associated anaplastic large cell lymphoma" OR "BIA-ALCL") AND ("etiopathogenesis" OR "pathogenesis" OR "etiology") restricting data from 2013 until 2023, only the free full text available were included. Studies not written in English were excluded. Additional studies were retrieved from the lists of references of selected articles.

3. Overview of BIA-ALCL

3.1. Defining BIA-ALCL

Breast implant-associated anaplastic large-cell lymphoma (BIA-ALCL) is an uncommon type of non-Hodgkin T-cell lymphoma. It´s a specific type of anaplastic large-cell lymphoma (ALCL) associated with breast implants. Characterized by the presence of CD-30 positive and anaplastic lymphoma kinase (ALK) negative, this entity is relatively recent, firstly described in 1997 by Keech Jr. [4, 6], and is a rare lymphoproliferative disease.

Currently included in 2017 as a provisional entity in the revised 4th edition of the WHO classification of tumours of hematopoietic and lymphoid tissues and in 2019 in the 5th edition of the WHO classification of breast tumours (2019) this disease is mainly associated with texturized breast implants and is typically found in the tissue surrounding these medical devices. It is normally characterized by the abnormal growth of atypical cells within the fibrous capsule that surrounds the breast implants [7, 8, 10].

The range of time between implantation and BIA-ALCL development and diagnosis varies between 2 to 32 years with a mean time of 8-10 years [11, 13].

It is crucial to recognize that BIA-ALCL differs greatly from breast cancer in several ways and is mostly considered a lymphoma of the immune system [16]. It is extremely important to understand the anaplastic large cell lymphoma (ALCL) to comprehend the BIA-ALCL development and infer about the etiopathogenesis.

ALCL is a large T cell lymphoma with a strong expression of CD30 marker. The anaplastic characteristics like atypia and pleomorphism gives its designation and, unlike other types of lymphoma, there is no reference to the T-cell lineage on its name [3, 22].

The ALCL can be divided into two major groups, the ALK-positive or ALK-negative with approximately the same incidence. ALK-positive has a better prognosis with overall survival between 70-80% and is commonly found in paediatric population, on the other hand ALK-negative ALCL is a more aggressive tumour, common in adults and has a surveillance rate between 40-60% [22].

ALK- ALCL can be classified in systemic, primary cutaneous or breast implant associated based on the location and extension of the disease.

BIA-ALCL was firstly considered a provisional entity and was hardly distinguished from ALCL ALK- disease. Later on the year 2019 Di Napoli described in molecular terms the BIA-ALCL as an independent type of cancer for the first time [37] . Unlike ALCL, BIA-ALCL was characterized as a triple negative genotype lacking characteristic gene rearrangements in ALK, TP63 and DUSP22, normally found in other ALK negative lymphomas, making it a distinct entity [37].

3.2 Incidence and prevalence of BIA-ALCL

Based on the American Society of Plastic Surgeons in the year of 2023 there were 1358 cases reported of BIA-ALCL Worldwide, with estimated incidence rates ranging from 1 per 3817 patients to 1 in 30000 [30]. Based on the actual evidence the number of reported cases in the literature has increased substantially, for this reason it is believed that this disease was previously underdiagnosed and so the incidence rates can be much higher than estimated. Of the 1358 cases, 418 (30, 78%) were in the USA, around 14, 28% in Australia, 1 case in Portugal [28] and approximately 55% in the rest of the world cases [30] . Curiously, despite the number of cases being considerably lower than in USA, Australia is estimated to have a higher incidence (1:1000 to 1:10000) of BIA-ALCL.

There are some conflicting information regarding the cases involving smooth implants, for ASPS there are no cases confirmed of BIA-ALCL with this type of implants but for FDA there has been reported 37 cases but all this cases, except 1, had a previous background of textured implant. The exception mentioned previously had no trustable medical background. [29,30]. Most patients with this disease, when early detected, have excellent prognosis following the excision of the surrounding capsule and respective implant, it is believed that the mortality ratio for this malignance is as low as 5%, which is much lower than other neoplasic entities [4, 5, 14] .

3.3 Risk factors for BIA-ALCL

In the last two decades, BIA-ALCL has been in the spotlight of researchers due to its importance to plastic surgery and breast implant development. There are many risk factors to the development of BIA-ALCL. Loch-Wilkinson et al. studied BIA-ALCL development with different types of implants and found out that textured implants were associated with 85% of the cases, alongside with implant duration, which increases with time; location, which is higher in sub glandular position; and genetic features. These represent the risk factors that can influence the development of this outcome. This leads us to the main point of this monography, deepen on the etiopathogenesis of Breast Implant associated- Anaplastic Large Cell Lymphoma. [3, 5]

4. Etiopathogenisis of BIA-ALCL

4.1 Chronic inflammation

Despite the existence of innumerous theories about BIA-ALCL pathogenesis, it seems to be intrinsically related to the host's inflammatory chronic response to the implant shell more than the implant content [33]. As aforementioned, the majority of cases are associated with textured breast implants, which sustains the theory that some particles from this kind of implants can lead to persistent antigenic stimulation that can induce macrophages and T-cells to proliferation, conditioning an immune dysregulation in genetically susceptible patients [1, 3, 5]. Cell lines and tissue from patients with BIA-ALCL lack expression of cell surface TCR, either of downregulation or due to had never been expressed [1, 3, 5].

BIA-ALCL cases are mainly associated with a CD4+/CD25+/FOXP3* immunophenotype that are T cell-related genes, enriched in this type of lymphoma; there is also an upregulation of CCL18, CXCL14 and CCR6, which encode chemokines implicated in migration and differentiation of a specific leukocytes subdivision. CCR6 is mostly associated with immature dendritic cells, TH17 and Treg, playing an important role in inflammatory cellular migration. As well as CCR6, CCL18 is able to induce conversion of memory-T cells into Treg cells. CXCL14 is once more strictly crucial to promotion of Treg in stroke as long as having a role in other immune cell migration and antimicrobial immunity [24].

As CD30+ cells are present in this microenvironment, we can predict that there will be a chronic T-cell stimulation in BIA-ALCL development [19].

This process plays a vital role in the response to a foreign body in all patients who have breast implants, leading to macrophagic, polimorphonuclear and Th17/TH1 secretion of IL-6, IL-10 and other cytokines (IL-8, IL-17, TGF-β1, and INF-γ). This process induce a suppression of regulatory T cells that leads to connective tissue capsule formation by recruited fibroblasts around the implant, normally not thicker than 1mm [44], taking in

average 10-14 days [5, 17, 23, 42, 49]. Autocrine IL-6 production was also linked and identified as a tumorigenic driver in some B-cell lymphomas and other solid tumors [17]. Furthermore, BIA-ALCL cell lines were also found to secrete or express IL-13, a TH2 citokine associated to allergic inflammation. There were also eosinophils and mast cells in BIA-ALCL tissue with a strong cell-surface IgE that may lead to an allergic inflammation role in this disease etiophatogenesis [18, 22]. The mechanism above mentioned can result, after breast-implant positioning, in some cases, in deformation of the medical device. When the process of recruitment of fibroblasts is overexpressed, capsular contracture can be developed which is believed to be associated with BIA-ALCL [7]. The capsular contracture is the most frequent complication of breast implants with an incidence of 8 to 15% [46, 47, 48]. The continuous inflammatory drive results in oligo and monoclonal CD30+ activated T cells proliferation that induce a pro-inflammatory status by releasing pro-inflammatory cytokines [1, 3, 5] . To confirm the association with BIA-ALCL *Marshall E Kadin* et al. [31] suppressed CD30 in BIA-ALCL cell lines TLBR1 and TLBR2 cells and IL-13 production was decreased, reducing the allergic inflammation in BIA-ALCL [31] .

4.2 Bacterial Biofilm

Not only the implants but also some lipopolysaccharides from bacteria can induce a chronic pro inflammatory status resulting in T helper 1 stimulation. Specifically *Ralstonia spp.* and *pseudomonas spp*., which are GRAM- bacteria and strongly associated with development of BIA-ALCL probably due to lipopolyssacharide coat (LPS) that is a powerful trigger to the host immune system, or *Staphylococcus epidermidis*, Gram+ bacteria normally related to capsular contracture [10, 25, 45]. This complication was also

shown to be accelerated in the presence of *Staphylococcus aureus* as an independent variable [10, 12, 25, 42, 45]. The bacterial source may be either endogenous or introduced/induced during the surgery and can grow in the implant surface [12, 24]. As the surface is higher in textured implants, the biofilm and bacterial load can be 30 times larger than in smooth implants, being able to exceed a certain threshold value and result in chronic antigen stimulation in genetically predisposed individuals leading in recruitment of macrophages and myofibroblasts which contribute to the fibrous capsule formation around the medical device [17, 18, 25]. This mechanism can later on lead to capsular contracture, which incidence can be reduced by using povidone-iodine, gentamicin and cefazolin to wash the implant pocket, or conduce to a dysregulation of JACK/STAT3 pathway predisposing the development of CD30+/ALK- T cell clones [44]. These cells can evolve to BIA-ALCL in the subsequent years, normally 8 to 12 years after the implantation [1, 3, 5, 8, 17]. Recent studies also showed a linear correlation between bacterial load on capsular implant and proliferation of activated lymphocytes [28]. It was also confirmed a stronger linkage for CD4+T cells, which are also found in BIA-ALCL. Despite all the associations with *Ralstonia spp*., some studies developed by Walker et al. [26] shows that BIA-ALCL does not appear to have a distinct microbiome when confronted to normal capsules, this infection may only represent an opportunistic infection in a peri-tumoral region. For these reasons, host-bacteria interaction needs further research [17].

4.3 Breast implant texture

There are two main types of breast implants, saline and silicone gel implants. Each of them have a variety of shapes (round or anatomic) and textures (smooth or textured,

micro or macro-textured (actually removed from market)) allowing the plastic surgeon to choose the most indicated for each patient [9].

The saline and silicone gels implants have both a silicone shell in the outer layer. Each of these types of implants can be round or anatomic shape. Round implants are symmetrical which allows it to be smooth once the rotation will not cause any aesthetic defect on the results. On the other hand, the second one has a teardrop shape that allows a more natural shape, being normally textured to prevent the rotation of the implant once they are not symmetrical [21].

Currently there are four types of textured implants based on 3D to 2D surface area ratio (high >5, intermediate 3–5, low 2–3 and minimal <2) and surface roughness (high > 150, intermediate 75–150, low 25–75 and minimal <25) [35].

In a retrospective study, Magnusson et al. [6] concluded that the specific risk of development of BIA-ALCL outcome was 23,4 times higher in Silimed polyurethane (macro-textured type 4) compared with SILTEX (textured type 2) and 16,52 times higher with Allergan by BIOCELL (macro textured type 3) compared with Mentor by SILTEX (textured type 2). Although Allergan textured breast implants were subject to regulatory action in some countries, they were not entirely removed from the market worldwide. Due to the connection to an elevated risk of BIA-ALCL, the U.S. Food and Drug Administration (FDA) urged Allergan to recall specific types of textured breast implants and tissue expanders in July 2019. Other countries' regulatory bodies, including those in France, Canada, and Australia, also took steps to halt or curtail the sale of specific Allergan macro-textured implants. French guidelines of the regulatory entities were applied in the majority of European countries, Portugal followed this directives and halt this type of implants [4, 6, 9]. Recently, in 2021, SCHEER recognized as “sufficient evidence” assuming a causal relationship between textured breast implants and the

development of BIA-ALCL. [14]

In other hand, textured implants were meant to disrupt collagen fibers around the implant and hypothetically reduce capsular contracture, this type of implants were also designed to increase the coefficient of friction and stabilize the medical device. Although these benefits were verified in some, textured implants also promote the proliferation of T-cell CD3, CD4, CD29, CD45RO positive in the capsule that is also associated with the evidence of silicon-laden macrophages that also increase T-cell chemiotaxis [5,38]. As this kind of implants increase friction, using as base the observation of these effects in other prosthetic materials, there is evidence of macrophages and phagocytosis stimulation conducting to inflammatory status, which silicone particles seem to induce similar response in animal models with less response and, in the moment of the study, no relation with BIA-ALCL [26]. Further investigation should be taken abroad to infer with clarity about the mechanical friction role [2,5,6,8].

4.4 Genetic background

There were already some somatic mutations linked to BIA-ALCL nominally in chromosome 19p, where JAK protein is encoded and may help and play a role in JAK/STAT pathway. This pathway deregulation was present in 60% of BIA-ALCL cases and seems to be activated by textured implants alongside with the existence of mutations in SOCS1, TP53, MYC and DNMT3A already described in BIA-ALCL and believed to help to clarify this lymphoma pathogenesis [1,2,17,32]. To date, the only mutation on JAK1 found in BIA-ALCL was the JAK1 G1097V which increases function of JAK protein and consecutively excessive STAT3 phosphorylation. The JAK3 germline mutation V722I can lead to a positive feedback loop in JAK/STAT and as consequence,

it is considered a genetic predisposing factor for BIA-ALCL [2,12].

STAT-3 mutation can be found in 26% of the cases of BIA-ALCL and it may lead to the JAK/STAT signaling pathway through STAT3 phosphorylation, which is common in this disease [12, 15, 34]. 64% of this mutations occur in point S614R, which affects SH2 domain, leading STAT3 constitutive activation and phosphorylation of proteins [2, 12, 39, 40].

From a therapeutic approach this dependence of JAK/STAT pathway can be an attractive target and currently there are case studies reporting efficacy with the use of anti-CD30 antibody drug conjugated with brentuximab vedotin [18].

Recently, one study with 13 patients, showed that human leucocyte antigen allele A*26 was significantly lower expressed in BIA-ALCL individuals which can, with further studies, mean a genetic predisposition to BIA-ALCL development [7,17]. Not only with these allele but also with BRCA1/2 and TP53 mutation carriers, that causes a cancer-predisposing condition known as Li-Fraumeni syndrome, with breast implants appears to be associated with a higher risk of BIA-ALCL but future studies should be took abroad to exclude a striker follow-up in this patient category [14,25]. Another study conducted with 29 patients found a 94% copy number aberrations (CNA) in their DNA and a 66% percentage of losses at 20q.13.13 which was reported to be characteristic of BIA-ALCL [17, 26].

5. Clinical presentation and therapeutic approach of BIA-ALCL

Patients with a median age of 52 and around 8-10 years following breast implant placement are most likely to develop BIA-ALCL [20]. There are two main clinical presentation for this disease. A "late seroma", or malignant effusion around the implant, known as the typical one, affects roughly two thirds of patients, has an indolent history,

is typically detected in early stages, and has an excellent prognosis after complete capsulectomy. After this procedure, breast reconstruction should be discussed with healthcare group and performed if consensus between patient and surgeon is adquired. After tumour resection, Ultrasonography and CT or PET/CT scan must be also performed every 6 months for 2 years [20, 36].

One third of the patients with BIA-ALCL can experience a presentation including tumour mass, containing or not effusion (typically indicating tumour extension beyond the capsule), regional lymphadenopathy, breast ulceration, skin papules and systemic symptoms such fever, night sweat or fever, which are rare but have already been described. This kind of presentation represents the most aggressive type of this pathology and, most of the times, require a multimodal therapy involving mass and lymph nodes resection, systemic therapy per NCNN guidelines it may be considered RT for unresectable disease [20,23,25].

6. Diagnosis of BIA-ALCL

BIA-ALCL diagnosis can be exigent comprehending multidisciplinary approach. These management requires a teamwork between healthcare professionals, in diagnostic imaging, pathology, haematology/oncology, surgical oncology, radiation oncology, and plastic surgery. The most effective way to screen patients for BIA-ALCL is ultrasonography but Finding ALK-negative T cells in seroma fluid analyses inside the fibrous capsule that surrounds the breast implant, is the gold standard for diagnosis. Biopsy or resection should be also considered to confirm presence of pleomorphic tumour cells expressing CD30 and T cell lineage [33].

7. Concluding remarks

To the date of this review we concluded that, despite of the different existent theories, the majority of them can interact and, in our perception, infer that the most acceptable hypothesis resides in the unification of biofilm, implant texturing, chronic inflammation and genetic drive in the BIA-ALCL development.

The chronic antigen stimulation seems to be the main initiator character and driver on the process of lymphogenesis leading to the multifactorial etiology for the development of BIA-ALCL [17].

References:

1. Alotaibi, S., Hamadani, M., Al-Mansour, M., & Aljurf, M. (2021). Breast Implant-associated Anaplastic Large Cell Lymphoma. Clin Lymphoma Myeloma Leuk, 21(3), e272-e276. https://doi.org/10.1016/j.clml.2020.12.005

2. Zhang, X. R., Chien, P. N., Nam, S. Y., & Heo, C. Y. (2022). Anaplastic Large Cell Lymphoma: Molecular Pathogenesis and Treatment. *Cancers (Basel)*, *14*(7). https://doi.org/10.3390/cancers14071650

3. Pina-Oviedo, S., Ortiz-Hidalgo, C., Carballo-Zarate, A. A., & Zarate-Osorno, A. (2021). ALK-Negative Anaplastic Large Cell Lymphoma: Current Concepts and Molecular Pathogenesis of a Heterogeneous Group of Large T-Cell Lymphomas. Cancers (Basel), 13(18). https://doi.org/10.3390/cancers13184667

4. Lee, J. H. (2021). Breast implant-associated anaplastic large-cell lymphoma (BIA-ALCL). Yeungnam Univ J Med, 38(3), 175-182. https://doi.org/10.12701/yujm.2020.00801

5. Cuomo, R. (2021). The State of the Art about Etiopathogenetic Models on Breast Implant Associated-Anaplastic Large Cell Lymphoma (BIA-ALCL): A Narrative Review. J Clin Med, 10(10). https://doi.org/10.3390/jcm10102082

6. Magnusson, M., Beath, K., Cooter, R., Locke, M., Prince, H. M., Elder, E., & Deva, A. K. (2019). 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, 143(5), 1285-1292. https://doi.org/10.1097/PRS.0000000000005500

7. St Cyr, T. L., Pockaj, B. A., Northfelt, D. W., Craig, F. E., Clemens, M. W., & Mahabir, R. C. (2020). Breast Implant-Associated Anaplastic Large-Cell Lymphoma: Current Understanding and Recommendations for Management. Plast Surg (Oakv), 28(2), 117-126. https://doi.org/10.1177/2292550320925906

8. Deva, A. K., Turner, S. D., Kadin, M. E., Magnusson, M. R., Prince, H. M., Miranda, R. N., Inghirami, G. G., & Adams, W. P., Jr. (2020). Etiology of Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL): Current Directions in Research. Cancers (Basel), 12(12). https://doi.org/10.3390/cancers12123861

9. McKernan, C. (2021). Treating breast implant-associated anaplastic large cell lymphoma. JAAPA, 34(4), 47-51. https://doi.org/10.1097/01.JAA.0000735780.35691.e5

10. Quesada, A. E., Medeiros, L. J., Clemens, M. W., Ferrufino-Schmidt, M. C., Pina-Oviedo, S., & Miranda, R. N. (2019). Breast implant-associated anaplastic large cell lymphoma: a review. Mod Pathol, 32(2), 166-188. https://doi.org/10.1038/s41379-018-0134-3

11. Wang, Y., Zhang, Q., Tan, Y., Lv, W., Zhao, C., Xiong, M., Hou, K., Wu, M., Ren, Y., Zeng, N., & Wu, Y. (2021). Current Progress in Breast Implant-Associated

Anaplastic Large Cell Lymphoma. Front Oncol, 11, 785887. https://doi.org/10.3389/fonc.2021.785887

12. Bewtra, C., & Gharde, P. (2022). Current Understanding of Breast Implant-Associated Anaplastic Large Cell Lymphoma. Cureus, 14(10), e30516. https://doi.org/10.7759/cureus.30516

13. Kricheldorff, J., Fallenberg, E. M., Solbach, C., Gerber-Schafer, C., Rancso, C., & Fritschen, U. V. (2018). Breast Implant-Associated Lymphoma. Dtsch Arztebl Int, 115(38), 628-635. https://doi.org/10.3238/arztebl.2018.0628

14. Santanelli di Pompeo, F., Clemens, M. W., Atlan, M., Botti, G., Cordeiro, P. G., De Jong, D., Di Napoli, A., Hammond, D., Haymaker, C. L., Horwitz, S. M., Hunt, K., Lennox, P., Mallucci, P., Miranda, R. N., Munhoz, A. M., Swanson, E., Turner, S. D., Firmani, G., & Sorotos, M. (2022). 2022 Practice Recommendation Updates From the World Consensus Conference on BIA-ALCL. Aesthet Surg J, 42(11), 1262-1278. https://doi.org/10.1093/asj/sjac133

15. Fitzal, F., Turner, S. D., & Kenner, L. (2019). Is breast implant-associated anaplastic large cell lymphoma a hazard of breast implant surgery? Open Biol, 9(4), 190006. https://doi.org/10.1098/rsob.190006

16. Xu, J., & Wei, S. (2014). Breast implant-associated anaplastic large cell lymphoma: review of a distinct clinicopathologic entity. Arch Pathol Lab Med, 138(6), 842-846. https://doi.org/10.5858/arpa.2013-0068-RS

17. Lajevardi, S. S., Rastogi, P., Isacson, D., & Deva, A. K. (2022). What are the likely causes of breast implant associated anaplastic large cell lymphoma (BIA-ALCL)? JPRAS Open, 32, 34-42. https://doi.org/10.1016/j.jpra.2021.11.006

18. Turner, S. D., Inghirami, G., Miranda, R. N., & Kadin, M. E. (2020). Cell of Origin and Immunologic Events in the Pathogenesis of Breast Implant-Associated Anaplastic Large-Cell Lymphoma. Am J Pathol, 190(1), 2-10. https://doi.org/10.1016/j.ajpath.2019.09.005

19. Shahriari, N., Ferenczi, K., & Heald, P. W. (2017). Breast implant-associated anaplastic large cell lymphoma: A review and assessment of cutaneous manifestations. Int J Womens Dermatol, 3(3), 140-144. https://doi.org/10.1016/j.ijwd.2017.05.005

20. Miranda, P., Moita, F., Vargas Moniz, J., & Rodrigues Dos Santos, C. (2022). Breast Implant-Associated Anaplastic Large Cell Lymphoma: Two Distinct Clinical Presentations. Acta Med Port, 35(11), 835-839. https://doi.org/10.20344/amp.16578

21. McKernan, C. D., Vorstenbosch, J., Chu, J. J., & Nelson, J. A. (2022). Breast Implant Safety: an Overview of Current Regulations and Screening Guidelines. J Gen Intern Med, 37(1), 212-216. https://doi.org/10.1007/s11606-021-06899-y

22. Turner, S. D. (2019). The Cellular Origins of Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL): Implications for Immunogenesis.

Aesthet Surg J, 39(Suppl_1), S21-S27. https://doi.org/10.1093/asj/sjy229

23. Stack, A., Ali, N., & Khan, N. (2020). Breast Implant-associated Anaplastic Large Cell Lymphoma: A Review with Emphasis on the Role of Brentuximab Vedotin. J Cell Immunol, 2(3), 80-89. https://doi.org/10.33696/immunology.2.025

24. Di Napoli, A., De Cecco, L., Piccaluga, P. P., Navari, M., Cancila, V., Cippitelli, C., Pepe, G., Lopez, G., Monardo, F., Bianchi, A., D'Amore, E. S. G., Gianelli, U., Facchetti, F., Berti, E., & Bhagat, G. (2019). Transcriptional analysis distinguishes breast implant-associated anaplastic large cell lymphoma from other peripheral T-cell lymphomas. Mod Pathol, 32(2), 216-230. https://doi.org/10.1038/s41379-018-0130-7

25. Alessandri-Bonetti, M., Jeong, T., Vaienti, L., De La Cruz, C., Gimbel, M. L., Nguyen, V. T., & Egro, F. M. (2023). The Role of Microorganisms in the Development of Breast Implant-Associated Anaplastic Large Cell Lymphoma. Pathogens, 12(2). https://doi.org/10.3390/pathogens12020313

26. Walker, J. N., Hanson, B. M., Pinkner, C. L., Simar, S. R., Pinkner, J. S., Parikh, R., Clemens, M. W., Hultgren, S. J., & Myckatyn, T. M. (2019). Insights into the Microbiome of Breast Implants and Periprosthetic Tissue in Breast Implant-Associated Anaplastic Large Cell Lymphoma. Sci Rep, 9(1), 10393. https://doi.org/10.1038/s41598-019-46535-8

27. Los-de Vries, G. T., de Boer, M., van Dijk, E., Stathi, P., Hijmering, N. J., Roemer,

M. G. M., Mendeville, M., Miedema, D. M., de Boer, J. P., Rakhorst, H. A., van Leeuwen, F. E., van der Hulst, R., Ylstra, B., & de Jong, D. (2020). Chromosome 20 loss is characteristic of breast implant-associated anaplastic large cell lymphoma. Blood, 136(25), 2927-2932. https://doi.org/10.1182/blood.2020005372

28. Cunha, A., Horta, R., & Barreiro, D. (2021). Epidemiological Profile in Portugal of Breast Implant-Associated Anaplastic Large Cell Lymphoma: A Cross-Sectional Study. Acta Med Port, 34(9), 572-579. https://doi.org/10.20344/amp.14055

29. U.S. Food and Drug Administration. Medical Device Reports of Breast Implant-Associated Anaplastic Large Cell Lymphoma. Medical Device Reports of Breast Implant-Associated Anaplastic Large Cell Lymphoma | FDA Accessed on the 12/06/2023

30. American Society of Plastic Surgeons. BIA-ALCL Physician Resources. BIA-ALCL Physician Resources | American Society of Plastic Surgeons (plasticsurgery.org) Accessed on 13/06/2023

31. Kadin, M. E., Morgan, J., Wei, W., Song, Z., & Yang, Y. (2023). CD30 Regulation of IL-13-STAT6 Pathway in Breast Implant-Associated Anaplastic Large Cell Lymphoma. Aesthet Surg J, 43(2), 137-146. https://doi.org/10.1093/asj/sjac234

32. Mehta-Shah, N., Clemens, M. W., & Horwitz, S. M. (2018). How I treat breast implant-associated anaplastic large cell lymphoma. Blood, 132(18), 1889-1898.

https://doi.org/10.1182/blood-2018-03-785972

33. Clemens, M. W., Nava, M. B., Rocco, N., & Miranda, R. N. (2017). Understanding rare adverse sequelae of breast implants: anaplastic large-cell lymphoma, late seromas, and double capsules. Gland Surg, 6(2), 169-184. https://doi.org/10.21037/gs.2016.11.03

34. Oishi, N., Brody, G. S., Ketterling, R. P., Viswanatha, D. S., He, R., Dasari, S., Mai, M., Benson, H. K., Sattler, C. A., Boddicker, R. L., McPhail, E. D., Bennani, N. N., Harless, C. A., Singh, K., Clemens, M. W., Medeiros, L. J., Miranda, R. N., & Feldman, A. L. (2018). Genetic subtyping of breast implant-associated anaplastic large cell lymphoma. Blood, 132(5), 544-547. https://doi.org/10.1182/blood-2017-12-821868

35. Mempin, M., Hu, H., Chowdhury, D., Deva, A., & Vickery, K. (2018). The A, B and C's of Silicone Breast Implants: Anaplastic Large Cell Lymphoma, Biofilm and Capsular Contracture. Materials (Basel), 11(12). https://doi.org/10.3390/ma11122393

36. George, E. V., Pharm, J., Houston, C., Al-Quran, S., Brian, G., Dong, H., Hai, W., Reeves, W., & Yang, L. J. (2013). Breast implant-associated ALK-negative anaplastic large cell lymphoma: a case report and discussion of possible pathogenesis. Int J Clin Exp Pathol, 6(8), 1631-1642. https://www.ncbi.nlm.nih.gov/pubmed/23923082

37. Longo, B., Di Napoli, A., Curigliano, G., Veronesi, P., Pileri, S., Martelli, M., De Vita, R., Felici, N., Cirillo, P., Bernardi, C., D'Orsi, G., Giacalone, M., Storti, G., & Cervelli, V. (2022). Clinical recommendations for diagnosis and treatment according to current updated knowledge on BIA-ALCL. Breast, 66, 332-341. https://doi.org/10.1016/j.breast.2022.11.009

38. Vorstenbosch, J., McCarthy, C. M., Shamsunder, M. G., Polanco, T. O., Dabic, S., Wiser, I., Matros, E., Dayan, J., Disa, J. J., Pusic, A. L., Cavalli, M. R., Encarnacion, E., Lee, M., Mehrara, B. J., & Nelson, J. A. (2021). Smooth versus Textured Implant Breast Reconstruction: Patient-Reported Outcomes and Complications. Plast Reconstr Surg, 148(5), 959-967. https://doi.org/10.1097/PRS.0000000000008411

39. Laurent, C., Nicolae, A., Laurent, C., Le Bras, F., Haioun, C., Fataccioli, V., Amara, N., Adelaide, J., Guille, A., Schiano, J. M., Tesson, B., Traverse-Glehen, A., Chenard, M. P., Mescam, L., Moreau, A., Chassagne-Clement, C., Somja, J., Escudie, F., Andre, M., Martin, N., Lacroix, L., Lemonnier, F., Hamy, A. S., Reyal, F., Bannier, M., Oberic, L., Prade, N., Frenois, F. X., Beldi-Ferchiou, A., Delfau-Larue, M. H., Bouabdallah, R., Birnbaum, D., Brousset, P., Xerri, L., & Gaulard, P. (2020). Gene alterations in epigenetic modifiers and JAK-STAT signaling are frequent in breast implant-associated ALCL. Blood, 135(5), 360-370. https://doi.org/10.1182/blood.2019001904

40. Blombery, P., Thompson, E. R., Jones, K., Arnau, G. M., Lade, S., Markham, J. F., Li, J., Deva, A., Johnstone, R. W., Khot, A., Prince, H. M., & Westerman, D.

(2016). Whole exome sequencing reveals activating JAK1 and STAT3 mutations in breast implant-associated anaplastic large cell lymphoma anaplastic large cell lymphoma. Haematologica, 101(9), e387-390. https://doi.org/10.3324/haematol.2016.146118

41. DePaola, N. E. K., & Coggins, H. (2019). Breast Implant-Associated Anaplastic Large Cell Lymphoma: What We Know. J Adv Pract Oncol, 10(1), 54-61. https://www.ncbi.nlm.nih.gov/pubmed/31308988
42. Adams, W. P., Jr., Haydon, M. S., Raniere, J., Jr., Trott, S., Marques, M., Feliciano, M., Robinson, J. B., Jr., Tang, L., & Brown, S. A. (2006). A rabbit model for capsular contracture: development and clinical implications. Plast Reconstr Surg, 117(4), 1214-1219; discussion 1220-1211. https://doi.org/10.1097/01.prs.0000208306.79104.18

43. Marques, M., Brown, S., Correia-Sa, I., MN, D. S. C., Rodrigues-Pereira, P., Goncalves-Rodrigues, A., & Amarante, J. (2012). The impact of triamcinolone acetonide in early breast capsule formation in a rabbit model. Aesthetic Plast Surg, 36(4), 986-994. https://doi.org/10.1007/s00266-012-9888-z

44. Adams, W. P., Jr., Rios, J. L., & Smith, S. J. (2006). Enhancing patient outcomes in aesthetic and reconstructive breast surgery using triple antibiotic breast irrigation: six-year prospective clinical study. Plast Reconstr Surg, 117(1), 30-36. https://www.ncbi.nlm.nih.gov/pubmed/16404244

45. Kossovsky, N., Heggers, J. P., Parsons, R. W., & Robson, M. C. (1984).

Acceleration of capsule formation around silicone implants by infection in a guinea pig model. Plast Reconstr Surg, 73(1), 91-98. https://doi.org/10.1097/00006534-198401000-00021

46. Mentor Corp. Saline implant PMA. Available at: www.fda. gov/cdrh/breastimplants/. Accessed October 1, 2000.
47. Inamed Corp. Saline implant PMA. Available at: www.fda. gov/cdrh/breastimplants/. Accessed October 1, 2000.
48. Inamed Corp. Silicone Gel Implant PMA. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfAdvisory/details.cfm?mtg388. Accessed June 1, 2003.
49. Broughton G 2nd, Janis JE, Attinger CE (2006) The basic science of wound healing. Plast Reconstr Surg 117:12S–34S

Apêndices

A. REPORTING GUIDELINES: SANRA Checklist - A scale for the quality assessment of narrative review articles

Scale for the Assessment of Narrative Review Articles – SANRA

Please rate the quality of the narrative review article in question, using categories 0–2 on the following scale. For each aspect of quality, please choose the option which best fits your evaluation, using categories 0 and 2 freely to imply general low and high quality. These are not intended to imply the worst or best imaginable quality.

1) Justification of the article's importance for the readership

The importance is not justified. — 0
The importance is alluded to, but not explicitly justified. — 1
The importance is explicitly justified. — 2

2

2) Statement of concrete aims or formulation of questions

No aims or questions are formulated. — 0
Aims are formulated generally but not concretely or in terms of clear questions. — 1
One or more concrete aims or questions are formulated. — 2

2

3) Description of the literature search

The search strategy is not presented. — 0
The literature search is described briefly. — 1
The literature search is described in detail, including search terms and inclusion criteria. — 2

2

4) Referencing

Key statements are not supported by references. — 0
The referencing of key statements is inconsistent. — 1
Key statements are supported by references. — 2

2

5) Scientific reasoning

(e.g., incorporation of appropriate evidence, such as RCTs in clinical medicine)

The article's point is not based on appropriate arguments. — 0
Appropriate evidence is introduced selectively. — 1
Appropriate evidence is generally present. — 2

2

6) Appropriate presentation of data

(e.g., absolute vs relative risk; effect sizes without confidence intervals)

Data are presented inadequately. — 0
Data are often not presented in the most appropriate way. — 1
Relevant outcome data are generally presented appropriately. — 2

2

Sumscore 12

SANRA – explanations and instructions

This scale is intended to help editors assess the quality of a narrative review article based on formal criteria accessible to the reader. It cannot cover other elements of editorial decision making such as degree of originality, topicality, conflicts of interest or the plausibility, correctness or completeness of the content itself. SANRA is an instrument for editors, authors, and reviewers evaluating individual manuscripts. It may also help editors to document average manuscript quality within their journal and researchers to document the manuscript quality, for example in peer review research. Using only three scoring options, 0, 1 and 2, SANRA is intended to provide a swift and pragmatic sum score for quality, for everyday use with real manuscripts, in a field where established quality standards have previously been lacking. It is not designed as an exact measurement of the quality of all theoretically possible manuscripts. For this reason, the extreme values (0 and 2) should be used relatively freely and not reserved only for perfect or hopeless articles.

We recommend that users test-rate a few manuscripts to familiarize themselves with the scale, before using it on the intended group of manuscripts. Ratings should assess the totality of a manuscript, including the abstract. The following comments clarify how each question is designed to be used.

Item 1 – Justification of the article's importance for the readership

Justification of importance for the readership must be seen in the context of each journal's readership.
Consider how well the manuscript outlines the clinical problem and highlights unanswered questions or evidence gaps – thoroughly (2), superficially (1), or not at all (0).

Item 2 – Statement of concrete/specific aims or formulation of questions

A good paper will propose one or more specific aims or questions which will be dealt with or topics which will be reviewed.
Please rate whether this has been done thoroughly and clearly (2), vaguely or unclearly (1), or not at all (0).

Item 3 – Description of the literature search

A convincing narrative review will be transparent about the sources of information on which the text is based. Please rate the degree to which you think this has been achieved. To achieve a rating of 2, it is not necessary to describe the literature search in as much detail as for a systematic review (searching multiple databases, including exact descriptions of search history, flowcharts, etc.), but it is necessary to specify search terms, and the types of literature included. A manuscript which only refers briefly to its literature search would score 1, while one not mentioning its methods would score 0.

Item 4 – Referencing

No manuscript references all statements. However, those that are essential for the arguments of the manuscript – "key statements" – should be backed by references in all or almost all cases. Exceptions could reasonably be made for rating purposes where a key statement has uncontroversial face-validity, such as "Diabetes is among the commonest causes of chronic morbidity worldwide."
Please rate the completeness of referencing: for most or all relevant key statements (2), inconsistently (1), sporadically (0).

Item 5 – Scientific reasoning

The item describes the quality of the scientific point made. A convincing narrative review presents evidence for key arguments. It should mention study design (randomized controlled trial, qualitative study, etc), and where available, levels of evidence.
Please rate whether you feel this has been done thoroughly (2), superficially (1), or hardly at all (0). Unlike item 6, which is concerned with the selection and presentation of concrete outcome data, this item relates to the use of evidence and of types of evidence in the manuscript's arguments.

Item 6 – Appropriate presentation of data:

This item describes the correct presentation of data central to the article's argument. Which data are considered relevant varies from field to field. In some areas relevant data would be absolute rather than relative risks or clinical versus surrogate or intermediate endpoints. These outcomes must be presented correctly. For example, it is appropriate that effect sizes are accompanied by confidence intervals. Please rate how far the paper achieves this – thoroughgoingly (2), partially (1), or hardly at all (0). Unlike item 5, which relates to the use of evidence and of types of evidence in the manuscript's arguments, this item is concerned with the selection and presentation of concrete outcome data.

Reference
Baethge C, Goldbeck-Wood S, Mertens S: SANRA—a scale for the quality assessment of narrative review articles. Research Integrity and Peer Review (2019) 4:5
https://doi.org/10.1186/s41073-019-0064-8

Scale for the Assessment of Narrative Review Articles – SANRA

1) Justification of the article's importance for the readership

The importance is explicitly justified. 2

Page 14: "In summary, understanding the etiopathogeny of BIA-ALCL is essential for lymphoma research progress, early detection, correct diagnosis, efficient therapy, identification of risk factors, and creation of preventative methods. We can significantly advance patient outcomes and advance the general safety of breast implant surgeries by examining the fundamental causes and processes of BIA-ALCL".

2) Statement of concrete aims or formulation of questions

One or more concrete aims or questions are formulated. 2

Page 14: "In this review, we overview the current literature related to the etipathogenesis of BIA-ALCL.(…) We aim to explore and synthetize the latest findings on the aetiology of the BIA-ALCL and resume the current existent theories. We further discuss the most accepted theory and briefly discuss the disease presentation, diagnosis and therapeutics".

3) Description of the literature search

The literature search is described in detail, including search terms and inclusion criteria. 2

Page 15: "A literature search was performed in the PubMed database, using the following searching terms, ("breast implant-associated anaplastic large cell lymphoma" OR "BIA-ALCL") AND ("etiopathogenesis" OR "pathogenesis" OR "etiology") restricting data from 2013 until 2023, only the free full text available were included. Studies not written in English were excluded. Additional studies were retrieved from the lists of references of selected articles.".

4) Referencing

Key statements are supported by references. 2

Referencing was made for most relevant key statements (e.g. page 20: "Currently there are four types of textured implants based on 3D to 2D surface area ratio (high >5, intermediate 3–5, low 2–3 and minimal <2) and surface roughness (high > 150, intermediate 75–150, low 25–75 and minimal <25).[37].").

5) Scientific reasoning

(e.g., incorporation of appropriate evidence, such as RCTs in clinical medicine)

Appropriate evidence is generally present. 2

Appropriate evidence was generally presented for key arguments (e.g. page 21: "STAT-3 mutation can be found in 26% of the cases of BIA-ALCL and it may lead to the JAK/STAT signaling pathway through STAT3 phosphorylation, which is common in this disease. [13,16, 36]").

The type of evidence was frequently presented by mentioning the study design (e.g. page 20:

"In a retrospective study, Magnusson et al. [6] concluded that the specific risk in Silimed polyurethane (macro-textured type 4) was 23,4 times higher and 16,52 times higher with Allergan by BIOCELL (macro textured type 3) compared with Mentor by SILTEX (textured type 2).").

6) Appropriate presentation of data

(e.g., absolute vs relative risk; effect sizes without confidence intervals)

Relevant outcome data are generally presented appropriately.

2

Literature results were generally presented in an adequate, clear, and concise manner (e.g. page 20: " In a retrospective study, Magnusson et al. [6] concluded that the specific risk in Silimed polyurethane (macro-textured type 4) was 23,4 times higher and 16,52 times higher with Allergan by BIOCELL (macro textured type 3) compared with Mentor by SILTEX (textured type 2).)

Sumscore 12

B. *Aesthetic Plastic Surgery* Instructions for Authors

Aesthetic Plastic Surgery Instructions for Authors

Before Manuscript Submission

English Language Editing

Manuscripts must be written in English, and authors are urged to aim for clarity, brevity, and accuracy of information and language. All manuscripts must include a structured abstract. Authors whose first language is not English should have their manuscripts checked for grammar and stylistic accuracy by a native English speaker.

For editors and reviewers to accurately assess the work presented in your manuscript you need to ensure the English language is of sufficient quality to be understood. If you need help with writing in English you should:

- Ask a colleague who is a native English speaker to review your manuscript for clarity.
- Visit the Springer English language tutorial that reviews a number of grammatical rules that should be followed when writing in English.

Use a professional language editing service. Two such services are provided by our affiliates Nature Research Editing Service and American Journal Experts. Other services are available, and using either of the below is is not a requirement for publication in this journal and does not imply or guarantee that the article will be selected for peer review or accepted.

- Nature Research Editing Service
- American Journal Experts

If your manuscript is accepted it will be checked by our copyeditors for spelling and formal style before publication.

Ethical Responsibilities of Authors

This journal is committed to upholding the integrity of the scientific record. As a member of the Committee on Publication Ethics (COPE), the journal will follow the COPE guidelines on how to deal with potential acts of misconduct.

Authors should refrain from misrepresenting research results which could jeopardize their entire scientific endeavour. Maintaining the integrity of the research and its presentation can be achieved by following the rules of good scientific practice:

- The manuscript has not been submitted to more than one journal for consideration.
- The manuscript has not been published previously (partly or in full), unless the new work concerns an expansion of previous work; please provide transparency on the re-use of material to avoid the hint of text-recycling ("self-plagiarism").
- A single study is not split up into several parts to increase the quantity of submissions and submitted to various journals or to one journal over time (e.g. "salami-publishing").
- No data have been fabricated or manipulated (including images) to support your conclusions
- No data, text, or theories by others are presented as if they were the author's own ("plagiarism"). Proper acknowledgements to other works must be given (this includes material that is closely copied (near verbatim), summarized and/or paraphrased), quotation marks are used for verbatim copying of material, and permissions are secured for material that is copyrighted.

Crosscheck

Submissions to Aesthetic Plastic Surgery are now being checked for plagiarism via CrossCheck. CrossCheck, a multi-publisher initiative, screens published and submitted content for originality and detects instances of overlapping and similar text in submitted manuscripts. This will ensure that the journal is actively combating plagiarism and is publishing only original research.

Notes on Authorship

- Ensure that consent to publish has been received from all co-authors and responsible authorities at the institute/organization where the work has been carried out before the work is submitted.
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- Historical Notes
- Innovative Techniques
- Letter To The Editor
- Multimedia Articles
- Review Articles

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> **Double column**
> **Column + 1 gutter + sub-column**
> **Column**
> **Sub-column**

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These rules are valid for all layouts. The values for the global standard layouts are given in Table

6. **Layout**

	Double column	**Column + 1 gutter + sub-column**	**Column**	**Sub-column**	**Max. column length**
Global large	174 mm	129 mm	84 mm	39 mm	234 mm
Global medium	160 mm	118 mm	76 mm	34 mm	216 mm
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