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The association between breast implants and anaplastic large cell lymphoma - a comprehensive review

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ABSTRACT

Introduction and purpose: Recently, the topic of the incidence of breast implant-associated anaplastic large cell lymphoma has become very popular. The aetiology of the disease is not fully understood. Many women worldwide have undergone breast implant surgery, so raising awareness about the possibility of developing BIA-ALCL is crucial for early diagnosis.
The aim of this article is to review and compile the currently available knowledge regarding the association of anaplastic large cell lymphoma with breast implants in patients who have undergone implant plastic surgery.

Brief description of the state of knowledge: Literature data indicate a multifactorial aetiology of BIA-ALCL. Textured surface breast implants are suspected to be a significant risk factor, as they may lead to the development of chronic inflammation. The most common symptoms of BIA-ALCL include the accumulation of serous fluid around the breast implant, pain, swelling or breast asymmetry. A proper diagnostic and therapeutic process improves the prognosis.

Material and methods: A comprehensive literature review was conducted using PubMed and Google Scholar databases. The search strategy was based on the following terms: BIA-ALCL; lymphoma; breast implants; textured implants.

Conclusions: Although BIA-ALCL is a rare disease, it is important to know the risk factors and clinical signs that may suggest the disease. A proper diagnostic process allows the disease to be detected at an early stage and treated effectively. Knowledge of the occurrence of potential complications of implant surgery allows patients to take informed consent and increases vigilance on the part of clinicians.

Key words: BIA-ALCL; lymphoma; breast implants; textured implants

Introduction

Breast Implant - Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) is a recently recognised non-Hodgkin's lymphoma, one of the subtypes of T-cell lymphoma. Anaplastic large cell lymphoma (ALCL) accounts for approximately 1-3% of non-Hodgkin's lymphomas and 15% of T-cell lymphomas [1]. BIA-ALCL is associated with textured surface implants in patients with both aesthetic and reconstructive breast implant surgeries [2]. In 2016, the World Health Organisation (WHO) recognised the disease as a specific pathological entity. The WHO then divided anaplastic large cell lymphoma into four groups: 1) ALK-positive ALCL (ALK+ALCL), 2) ALK-negative ALCL (ALK-ALCL), 3) primary cutaneous ALCL (pcALCL), and 4) breast implant associated ALCL (BIA-ALCL). These four types have different clinical manifestations, genetic mutations, prognosis and treatment [1]. BIA-ALCL is characterised as CD30 positive and anaplastic lymphoma kinase (ALK) negative [3]. Estimating the risk of developing BIA-ALCL due to breast implant exposure is challenging and based on approximate data concerning patients at risk [4]. This topic is highly prevalent among plastic surgery specialists. Over the past few years, numerous publications regarding this condition have emerged [5].

The analysis of the topic and the collection of data serve to better understand the disease in terms of causes and risks of incidence, and how to optimise the safety of women who require or desire breast implants [5]. It is important to raise awareness among women planning this surgery about the risk of possible complications.

Aetiology

The aetiology of the disease is not fully elucidated. There are several theories that point to a multifactorial aetiology [2]. The most popular one relates to the presence of bacterial microbiome around the implant. This acts as a chronic inflammatory stimulus, causing the activation of T lymphocytes, and subsequently their transformation, ultimately leading to the development of BIA-ALCL [5]. This theory mainly applies to implants with a textured-surface, which exhibit a greater ability for bacterial adhesion on their irregular outer surface. Bacteria adhere much less readily to implants with a smooth outer surface, so smooth-surfaced implants have a lower tendency to support the microbiome [2]. Ralstonia pickettii is an example of a bacterium found in unexpectedly high numbers around damaged implant

capsules. Other hypotheses related to the aetiology of BIA-ALCL involve the fragmentation of particulate matter from the implant shell, which also pertains mainly to textured implants, the presence of heavy metals in the manufacturing process, and the occurrence of specific genetic predispositions. It is speculated that ultimately, a combination of multiple factors, including the passage of time, leads to the development of the disease [5].

Implant surface

Breast implant associated anaplastic large cell lymphoma is mainly associated with textured surface implants [2]. However, it is unclear whether cases have been identified involving entirely smooth surface implants, and ultimately, such a possibility cannot be ruled out. Given that textured surface implants are clearly the predominant risk factor, attempts have been made to quantitatively determine the risk of the disease depending on the degree of texturization. Implant surfaces have been divided and classified into four groups: group 1 - smooth implants, group 2 - microtexture, group 3 - macrotexture, group 4 - polyurethane-coated implants. It has been observed that BIA-ALCL is primarily associated with groups 3 and 4 of implants. The theory is that the more textured the surface of the implant, the higher the frequency of BIA-ALCL occurrence [5]. The surface from group 4 is characterized by the highest roughness, which enhances the growth of both Gram-positive and Gram-negative bacteria. Bacterial growth and T-cell activation occur much faster on this surface [2]. In 1968, polyurethane coatings were first introduced to breast implants [7]. The purpose of such surfaces was to prevent the organized arrangement of myofibroblasts, reducing the risk of capsular contracture [2]. After some time of using these implants in patients, a link was found between polyurethane and the carcinogenic compound 2,4-toluenediamine, leading to the withdrawal of these implants in the United States. Further research showed that the level of 2,4-toluenediamine is equivalent to occupational exposure, thus likely posing minimal risk to patients. Outside of the United States, polyurethane-coated implants are still used [7]. Some clinical evidence has demonstrated the effectiveness of these implants in reducing one of the postoperative complications - capsular contracture. However, variable techniques and length of observation must be considered. It has been shown that smooth surfaced breast implants placed in the subfascial plane have a higher risk of developing capsular contracture compared to textured implants. However, when comparing smooth and textured surface implants placed in the submuscular plane, no differences in the frequency of occurrence of this complication were observed [8]. A 30-year study found that the incidence of capsular contracture increases

after 10 years with polyurethane-coated implants, as degradation and phagocytosis of the polyurethane coating occur. Therefore, the benefits compared to the risks of using polyurethane coatings in implants must be prospectively investigated to obtain better clinical data regarding their effectiveness and safety [7].

Risk of illness

The determination of the frequency of BIA-ALCL occurrence is controversial and extremely challenging, as literature reports vary significantly, ranging from 1 in 300/400 cases to 1 in 100,000/200,000 cases. Poor data regarding global sales volume and the lack of precise registries make it difficult to quantitatively estimate the risk of disease occurrence [5]. There are several limitations in estimating the actual frequency of occurrence and the risk of developing BIA-ALCL. One must be aware of the prevalence of women with breast implants and the type of implant inserted (smooth or textured surface); however, the problem lies in the lack of detailed reports and the growing phenomenon of cosmetic tourism [9]. There is also a lack of reports regarding adverse events associated with breast implants [10]. It is estimated that globally around 1.5 million women receive breast implants annually, with approximately 450,000 in the United States [11]. The number of cases of BIA-ALCL is increasing; however, this may be a consequence of the steadily growing awareness in diagnosing this new pathological entity [10]. In addition, most surgeons use the products of one or two manufacturers, and much more is known about the individual risks of each manufacturer, so it is more reasonable to talk about the risks of implants from a specific manufacturer [5]. Cases of BIA-ALCL in patients following breast implant surgeries have raised concerns regarding the long-term safety of implants [10]. Consequently, breast implants have been placed on the list of high-priority substances for evaluation by the International Agency for Research on Cancer (IARC) for inclusion in the human carcinogenic risk monograph [12].

Genetic predisposition

The risk of developing BIA-ALCL due to exposure to breast implants is estimated based on approximate data. There is increasing evidence confirming that the presence of specific mutations in patients' germline may be associated with the occurrence of BIA-ALCL. This fact increases interest in possible genetic markers of predisposition to this type of lymphoma. Literature data indicate that patients with a genetic predisposition to breast cancer, mainly in terms of the presence of mutations in the germline TP53 and BRCA1, BRCA2,

simultaneously show a higher tendency to develop BIA-ALCL. These high-risk patients are already covered by strict surveillance programs, allowing for the detection of the disease in its early stages, thus no need for alternative approaches in postoperative monitoring has been identified [4]. Mutations in genes associated with the JAK/STAT signaling pathway may also be relevant in this type of lymphoma [13].

Clinical manifestations

The average age of patients at the time of BIA-ALCL diagnosis is around 50 years, and the average time from breast implant surgery to disease diagnosis is approximately 7-10 years. The most common symptoms of BIA-ALCL include the presence of seroma fluid around the breast implant (mainly those with textured surfaces), pain, breast swelling or asymmetry. Capsular contracture may also occur, and in some cases, there may even be a breast mass with lymph node involvement [14]. A small number of patients (10-20%) develop a tumour mass with possible lymph node involvement [10]. In some cases, skin lesions (erythema, skin papules), capsular contractures, serous tissue involvement, and B-symptoms (such as fever, lymphadenopathy, night sweating, and fatigue) have been reported at the time of diagnosis, but these with much lower frequency [14,15]. Rarely, cases with bilateral involvement of the breast capsule have been described; in most cases the complication is localised in one breast. The clinical picture at the time of diagnosis of the disease may have prognostic significance. Literature data indicate that the survival of patients diagnosed with BIA-ALCL in situ, without infiltration of the implant capsule, is significantly longer than in the case of BIA-ALCL infiltrating the capsule and adjacent tissues, as can occur with breast mass [10]. It has also been observed that involvement of regional lymph nodes, most commonly the axillary nodes, significantly worsens the prognosis [16]. BIA-ALCL affecting sites other than the ipsilateral breast and regional lymph nodes is classified as stage IV disease. There have been cases with involvement of the liver, small intestine, central nervous system and bone. Invasion of the thorax and mediastinum is associated with the highest risk of death [10].

Diagnostics

The prognosis of BIA-ALCL is very favourable if identified quickly and treated consistently [17]. A stage of the disease with infiltration that cannot be completely cured by surgical methods has a much worse prognosis and a higher mortality rate [18]. In view of this, awareness of the disease in patients and a proper diagnostic process are very important [19].

The diagnosis of BIA-ALCL should be performed in clinical units demonstrating the necessary knowledge of the correct diagnostic algorithm. Assessment should include clinical examination, imaging and biopsy [20]. Attention should be paid to a detailed medical history, especially regarding the patient's family history of cancer, as this may indicate the need to refer the patient for genetic testing for specific mutations [20, 21].

Imaging diagnosis is of great importance in detecting BIA-ALCL; however, imaging of this type of lymphoma can be challenging due to its non-specific appearance [20]. According to the 2021 National Comprehensive Cancer Network guidelines, when suspicion of BIA-ALCL arises due to the occurrence of specific symptoms, the initial step in evaluation should be ultrasonography [22, 23]. This is the examination of choice to assess pain, swelling or tumour associated with the breast implant [20]. In addition, this examination should assess the implant on the opposite side, if present, and any enlargement of the axillary lymph nodes [24]. Knowledge of the type of implant significantly facilitates ultrasound assessment and reduces the risk of incorrect interpretations [20].

If ultrasonography raises suspicion of disease or is inconclusive or indicates implant rupture, magnetic resonance imaging (MRI) should be performed [22, 20]. MRI has the highest sensitivity in assessing suspected lymphoma and evaluating implant integrity, so its use is widespread in clinical practice [22, 25]. MRI is also useful for assessing the extent of the disease and planning the scope of surgery if a diagnosis has been established based on an initial fine-needle aspiration or core biopsy [20].

PET/CT also plays an important role in the imaging diagnosis of BIA-ALCL. It is used before surgical intervention and in assessing the response to systemic treatment [20, 24, 26]. Mammography has low sensitivity and specificity for BIA-ALCL, but is used to assess potential lesions, especially in patients over 40 years of age [20].

The diagnosis of the disease is also based on the cytological, immunohistochemical and histopathological evaluation of the effusion sample or, less commonly, a biopsy of the mass. This allows for the detection of pleomorphic CD30+ lymphocytes that are negative for the anaplastic lymphoma kinase (ALK) receptor [27].

If fluid accumulates around the implant, a fine-needle aspiration should be performed under ultrasound guidance to avoid damaging the implant. Immunohistochemical testing for CD30 is crucial for diagnosing BIA-ALCL; however, as an isolated test, it is not sufficient because CD30+ lymphocytes can also be observed in non-neoplastic effusions. Only the presence of more than 10% large CD30+ cells with atypical morphology in the fluid raises suspicion of

BIA-ALCL. Additionally, other markers, such as ALK protein negativity, should also be examined [22, 28]. Most effusions around implants are not related to ALCL; however, it is important to be aware of the limitations of diagnostic tests and the possibility of obtaining false-negative results [20].

After confirming the diagnosis, the patient should be referred to the breast disease unit for a multidisciplinary evaluation. This integrated approach is helpful in selecting the most effective and optimal treatment for the patient [27].

Treatment

Surgical treatment is the primary approach for patients with confirmed BIA-ALCL. Patients with locally advanced disease or distant metastases may benefit from initial systemic therapy [20].

After confirming BIA-ALCL in examinations, treatment for the disease confined to fluid accumulation or the capsule involves surgical removal of the implant and complete capsulectomy [29]. Complete surgical excision limits disease progression and future recurrences, as well as improves prognosis. During a total en-bloc capsulectomy, the entire element encompassing the whole capsule and associated mass is removed. Thus, the implant and any associated effusion are entirely contained within the removed specimen [20]. If a tumour mass is present, confirmed by imaging, the tumour mass should be completely removed with confirmation that the surgical margins are not occupied by malignant disease [29]. Pneumothorax poses some perioperative risk, as the capsule of subpectoral implants can adhere closely to the surface of the ribs or intercostal muscles [20]. Additionally, excisional biopsy of suspicious lymph nodes found during surgery should be performer [29]. Sometimes, enlargement of axillary lymph nodes can occur due to silicone lymphadenopathy [30]. After complete excision, the capsule should be submitted for histopathological examination to assess the extent of lymphoma involvement. If the disease is at a limited stage, there is no need for postoperative chemotherapy or radiotherapy. Complete surgical excision of the lesion ensures complete remission of the disease [29]. In patients with positive surgical resection margins indicating residual tumour, supplementary chemotherapy and immunotherapy should be administered. If residual disease is present in the patient, the multidisciplinary team should consider recommending postoperative radiotherapy as an adjunct to chemotherapy or immunotherapy [22]. National Comprehensive Cancer Network guidelines recommend the use of local radiotherapy for localised residual disease in patients

who are not eligible for surgery [29]. For patients with disseminated disease, appropriate systemic treatment should be initiated. In all cases of BIA-ALCL advancement, patients should be managed and monitored by a multidisciplinary team [22]. Additionally, it is worth considering removal of the implant in the contralateral breast, as cases of bilateral occurrence of BIA-ALCL have been reported [29].

Currently, there are no guidelines indicating when or whether breast implants should be replaced. This is a topic that requires further research, so it is important to report each diagnosis of BIA-ALCL in order to develop accurate statistics and clarify guidelines for the diagnosis and management of this type of cancer [22, 29].

Breast reconstruction after BIA-ALCL diagnosis

In literature, there is no consensus on the timing of breast reconstruction following the diagnosis of BIA-ALCL [22, 32]. There are reports suggesting that immediate autologous reconstruction can be performed in patients with localized disease, whereas in patients with disseminated disease or without radically resectable lesion, delayed reconstruction should be considered after repeat imaging studies [20, 22]. This is a controversial topic that requires further research [29]. Methods that can be considered include autologous flaps, fat grafting and even reconstruction with implants [20]. Reconstructions with implants, especially textured implants, should be avoided to prevent the development of inflammation caused by the textured surface, which could initially lead to the development of BIA-ALCL [29]. A multidisciplinary team approach is essential for the proper management of this disease [22].

Post-treatment monitoring

After completing treatment, patients with BIA-ALCL should undergo clinical and radiological follow-up to monitor for disease recurrence. The National Comprehensive Cancer Network guidelines recommend assessing patients at least every 3-6 months for 2 years, and then as indicated thereafter [20, 29]. It is recommended to undergo imaging studies every 6 months for a period of 2 years after completing treatment, with preferred methods being contrast-enhanced computed tomography (CT) of the chest, abdomen and pelvis or positron emission tomography (PET) scan [29]. However, due to factors such as the costs of postoperative imaging and limited evidence of the benefits of imaging surveillance, recent UK guidelines do not recommend routine imaging after successful surgical treatment of BIA-ALCL. Clinical

judgment should guide decision-making. Various practices and management schemes are reported worldwide [31].

Prognosis

Early diagnosis of the disease significantly increases the chance of successful surgery with curative intent and improves long-term prognosis [20]. The prognosis of disease confined to the effusion or to the capsule is excellent provided appropriate therapeutic management. The early stage of the disease affects a significant majority of patients. After complete surgical removal of the implant and capsule, approximately 93% of patients achieve complete remission after a two-year follow-up period [20, 29]. Tumour extending beyond the capsule, with lymph node involvement, indicate an aggressive course of the disease and is associated with a poorer prognosis [20, 33]. An unfavorable prognostic factor is the presence of tumor cells infiltrating the chest wall, which complicates the performance of radical surgical procedure [22].

The rapid spread of information about the incidence of BIA-ALCL has caused anxiety and confusion among patients, especially those who have undergone mastectomy due to breast cancer or prophylactic mastectomy due to a genetic mutation with implant reconstruction. Negative emotions are particularly associated with women who have previously experienced breast cancer [34].

Conclusions

Although BIA-ALCL is a rare disease, knowledge about it is essential for both doctors and patients undergoing breast implant surgery. It is important to be aware of the risk factors and clinical symptoms that may suggest the presence of the disease. Textured surface breast implants are considered a significant risk factor. A proper diagnostic process allows for the detection of the disease at an early stage, which greatly improves the prognosis. A multidisciplinary team approach is crucial for the proper treatment process of this pathology. Further research is necessary to issue up-to-date guidelines and protocols for patients with BIA-ALCL. Awareness of potential complications in patients after breast implant surgery allows for informed consent by patients and increases vigilance among doctors.

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