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Breast implant-associated anaplastic large cell lymphoma

CLINICAL REVIEW

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Breast implant-associated anaplastic large cell lymphoma is a subtype of non-Hodgkin's lymphoma that can occur around the surface of textured breast implants or in patients who have previously had textured breast implants. The condition should be suspected in cases of late-onset breast asymmetry and seroma formation around a breast implant. If the implant and surrounding connective tissue capsule is removed, the prognosis is usually very good. The purpose of this clinical review article is to provide a brief overview of the diagnosis and treatment of breast implant-associated anaplastic large cell lymphoma.

Since 1962, breast implants have been used for cosmetic procedures and reconstruction after breast cancer. The first generation of breast implants were teardrop-shaped and consisted of a smooth-surfaced silicone shell filled with silicone gel (1). Capsular contracture, where a thickened fibrous capsule formed around the implant, was common, leading to a hard and tender breast (2). The smooth surface of the silicone shell meant that the implant could rotate, which gave the breast an unnatural appearance. The first implants were therefore equipped with Dacron patches to fix the implant to the chest wall. The bonding of the patches to the implant was a weak point that could lead to rupture of the outer shell, and this solution was abandoned. Efforts were made to improve the implants by using silicone fillers with various properties and other types of fillers, such as saline, methylcellulose and oil (3). The challenges relating to capsular contracture, rotation and rupture were addressed by modifying the outer shell of the implants. In the 1970s, implants were developed where the silicone shell was covered with rough-textured polyurethane foam. The textured surface created friction between the implant and the surrounding scar capsule, preventing rotation and leading to the formation of a non-linear surface of collagen fibres in the capsule, which reduced the incidence of contractures. Implants with textured surfaces of the silicone shell were introduced in the 1980s. In the 1980s and 1990s, concerns about a possible association between silicone filler leakage and connective tissue diseases led to a ban on the use of silicone-filled breast implants in the United States in 1992. This ban was lifted in 2006 (4–6).

Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is a rare variant of T-cell lymphoma that was first described in 1997. The first known case involved a 41-year-old woman who had received textured silicone shell breast implants filled with saline five years earlier. She developed a rare type of

non-Hodgkin's lymphoma, ALCL, in one breast. The authors concluded that a causal relationship between the breast implant and this type of cancer could not be established with certainty (7). In 2011, the US Food and Drug Administration (FDA) published a report based on 18 studies from the period 1997–2010, which included a total of 34 cases of ALCL in women with breast implants. The report concluded that there was a possible association between ALCL and breast implants (8). In a collaboration between the FDA and the American Society of Plastic Surgeons, a registry of patients diagnosed with BIA-ALCL was established in 2012 (9). In 2016, this cancer type was classified as a separate lymphoma by the World Health Organization (WHO) (10). Unlike breast cancer, which arises in the breast parenchyma, BIA-ALCL occurs around the surface of textured breast implants and is usually detected by aspirating fluid from the seroma cavity between the implant and the surrounding fibrous connective tissue capsule (Figure 1).

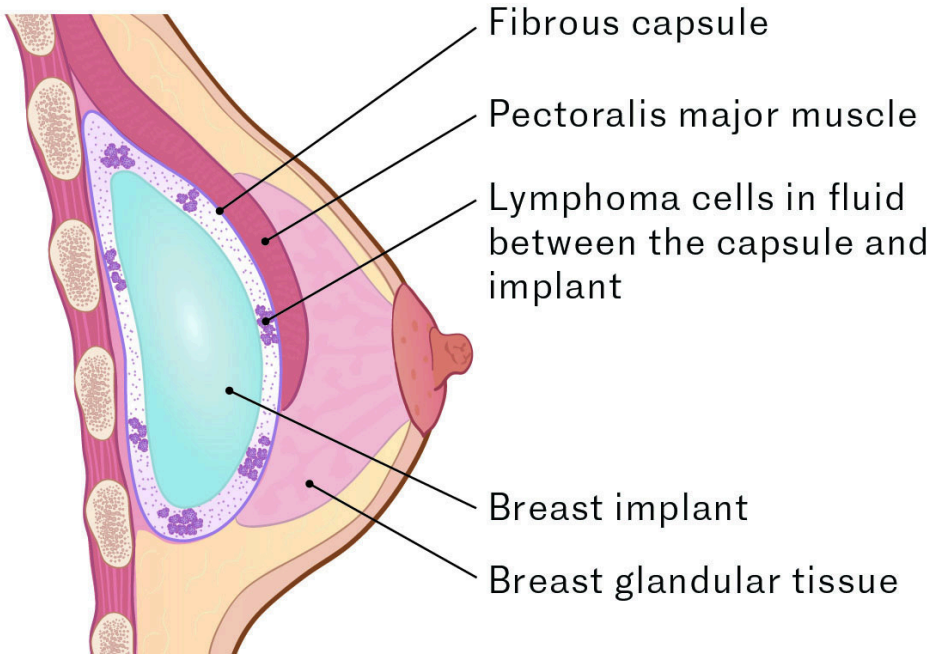

Figure 1 The illustration shows a breast with an implant located under the pectoralis major muscle and BIA-ALCL located in the fluid between the surface of the implant and the fibrous connective tissue capsule. Illustration: Jeanette Engqvist / Illumedic.

The purpose of this article is to present up-to-date knowledge on the aetiology, pathogenesis and incidence of BIA-ALCL, as well as the evaluation process for suspected cases. The article is based on consensus-based guidelines, a literature review and the authors' clinical experience.

Aetiology and pathogenesis

The aetiology of BIA-ALCL is not fully understood. Chronic inflammation, the texture of the implant's outer shell, biofilm and genetic factors have been suggested as contributory causes (11). The type of filler in the implant does not appear to be significant. According to the ISO classification of breast implant

properties, implant surfaces are defined as smooth and with an average surface texture of less than 10 µm, microtextured from 10 to 50 µm, and macrotextured over 50 µm (12).

In a 2015 study reviewing 173 cases of BIA-ALCL, all patients for whom information on the type of implant was available had implants with a macrotextured surface. The authors concluded that the cause was multifactorial chronic inflammation associated with textured implants (13). Different processes take place to create varying degrees of texture in the silicone shell of the implant, and it has been debated whether the texture itself or the method by which the texture is created is the reason for the association between textured implants and BIA-ALCL (13).

A study from 2017 claimed that bacterial contamination and biofilm resulting from suboptimal surgical technique, rather than the surface of the implant, were the cause of this condition (14, 15). However, this study has been criticised for poor scientific quality and for the authors' financial links to a producer of macrotextured implants (16). In recent years, the biofilm hypothesis has taken a back seat, and a causal relationship between macrotextured implants and BIA-ALCL is considered established (17).

In an Australian registry-based study of 104 cases diagnosed between 2015 and 2019, a higher incidence was found in women with rough-textured implants compared to microtextured implants (18). No cases of ALCL have been reported for implants with a smooth surface (19). At the request of the FDA, macrotextured implants were withdrawn from the market in 2019 (20).

There has been discussion about whether women with a genetic predisposition to breast cancer have an increased risk of BIA-ALCL (21, 22). This particularly applies to women with mutations in the BRCA1 and BRCA2 genes, who have an increased risk of breast cancer and are therefore offered risk-reducing bilateral mastectomy. This group of women is typically offered reconstruction with implants (23). In a 2020 study from the Netherlands involving 49 women with BIA-ALCL, an increased prevalence of BRCA1 and BRCA2 mutations was found (21). It is unclear whether genetic markers have prognostic value, and genetic testing is not recommended outside of studies (19).

Incidence

The lack of reliable figures for the number of patients with implants or the number of implants sold makes it difficult to determine the incidence of BIA-ALCL. In previous studies, the incidence was estimated to be between 1: 500 000 and 1: 3 000 000 (13). In a 2021 study of incidence across 48 European countries with 43 confirmed cases, the number of reported cases per 1 000 000 inhabitants varied from 4.12 in the Netherlands to 0.05 in Turkey (24). In more recent, smaller population-based studies, the incidence has been estimated at 1 in 300 (25–27). As of June 2023, the FDA had registered 1246 confirmed cases and 63 deaths from this condition worldwide (28). In Norway, 14 women diagnosed with BIA-ALCL are registered in the national quality registry for lymphoid malignancies for the period 2010–2023 (29).

Diagnostics

BIA-ALCL is diagnosed by the presence of anaplastic cells in cytological examination of seroma fluid or histological examination of specimens following capsulectomy. Immunohistochemistry shows that the malignant cells are positive for the marker CD30 and negative for the marker ALK-1 (anaplastic lymphoma kinase) (30). The condition is associated with both silicone and saline implants and should be suspected in women with textured implants who present with spontaneous swelling of the breast or a mass in the breast area that occurs one year or more after implantation (Box 1) (31). The median time from implantation to diagnosis is nine years (9). In our experience at Radiumhospitalet, a large number of women report rapid changes in breast size, often during the course of a day.

Box 1 Symptoms of BIA-ALCL (31).

Swelling of a breast more than one year after implantation of a textured breast implant

Recently developed breast asymmetry

Palpable tumour in or near the breast

Pain

Redness of the skin

Guidelines for the diagnosis and treatment of BIA-ALCL are based on multidisciplinary consensus. The National Comprehensive Cancer Network developed consensus-based guidelines for diagnosis and treatment in 2016, and these have been incorporated into the guidelines for T-cell lymphomas. Figure 2 shows the proposed diagnostic workup in cases of clinical suspicion of this condition based on the latest version of these guidelines (31). In cases of clinical suspicion of BIA-ALCL, the patient should be referred to a breast diagnostic centre for ultrasound examination of the breast and axilla, with a focus on periprosthetic fluid, tumours in the breast, or enlarged regional lymph nodes. Suspicion of BIA-ALCL must be indicated on the referral. If fluid is found around the implant, at least 50 ml of fluid should be aspirated for diagnostic cytology and preparation of a cell block. Periprosthetic fluid should be sent for diagnostic examination upon first aspiration because recurring seroma can cause a dilution effect, which may result in a false negative cytological examination. If a tumour is found, a biopsy should be taken (31).

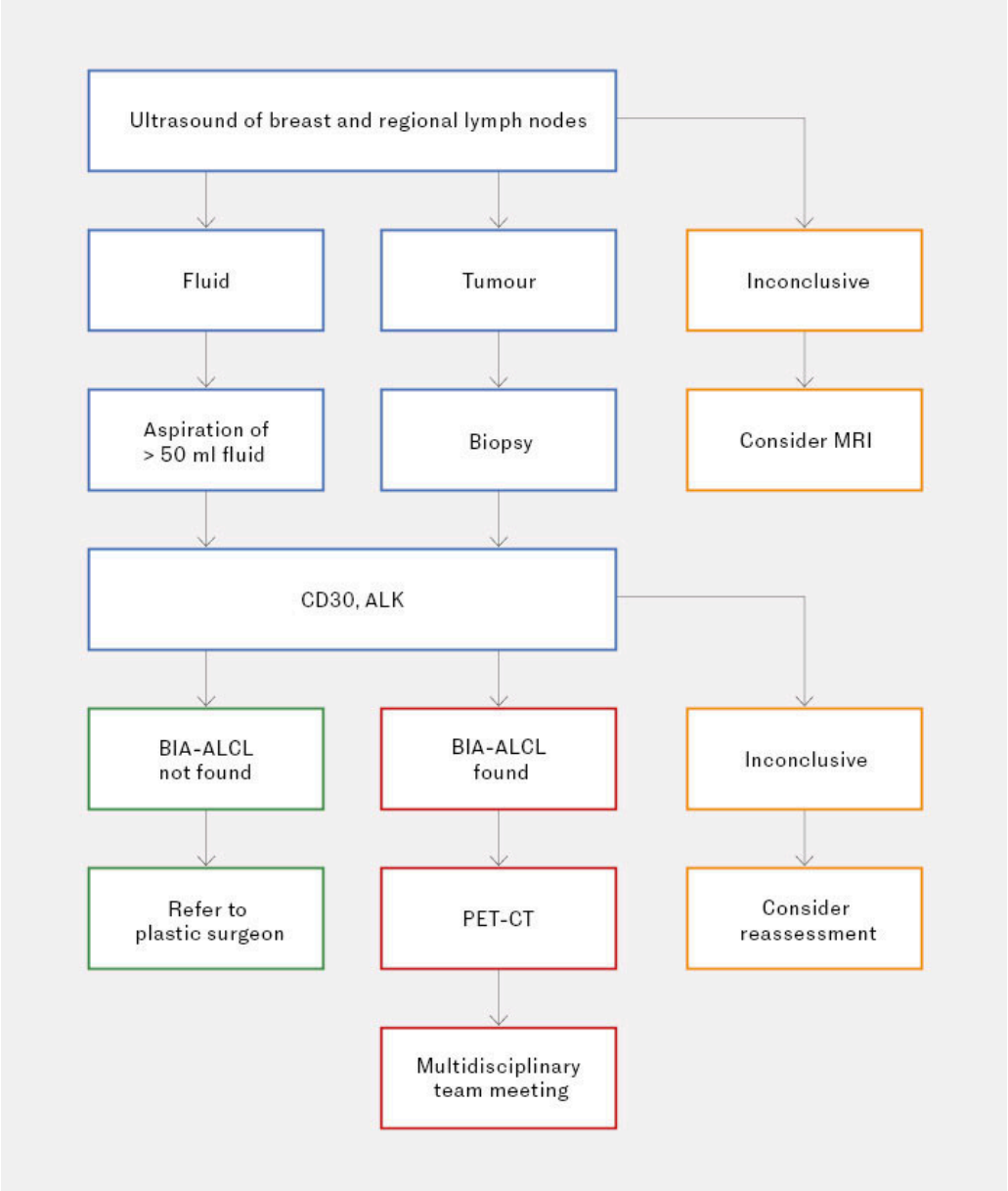

Figure 2 Flowchart for the diagnosis of suspected BIA-ALCL. The figure is based on the National Comprehensive Cancer Network's guidelines (31). ALK: anaplastic lymphoma kinase; BIA-ALCL: breast implant-associated anaplastic large cell lymphoma; MRI: magnetic resonance imaging; PET: positron emission tomography.

In cases of confirmed BIA-ALCL, preoperative staging with PET-CT should be performed, and the patient should be referred to a multidisciplinary team with experience in the condition. The team should consist of a plastic surgeon, oncologist and pathologist. If the findings are unclear, re-examination of the cell block from the aspirate should be considered by a pathology department with experience in the condition. In cases of negative cytology, but with clinical or radiological suspicion of BIA-ALCL, the patient should be referred to a centre with expertise in the condition. The authors have observed cases where BIA-ALCL was found in the tissue removed during surgery after capsule removal based on clinical suspicion of the condition, even when the preoperative analysis of periprosthetic fluid only showed atypical cells with an inconclusive diagnosis.

Treatment and follow-up

The definitive treatment in most cases is total intact capsulectomy, where the implant capsule is removed as a single unit. The vast majority of patients are diagnosed at an early stage, with disease confined to periprosthetic fluid or infiltration in the capsule without invasion and without radiological evidence of involvement of locoregional lymph nodes. These patients have a very good prognosis (32, 33). The condition occurs bilaterally in 5 % of patients, and prophylactic removal of the implant and capsule on the contralateral side is recommended (34). Prophylactic removal of macrotextured implants in asymptomatic women is not recommended (19). Direct or delayed reconstruction with a smooth implant or autologous reconstruction can be considered (31).

An adaptation based on the TNM system is recommended for staging (34). After complete excision, patients must attend check-ups every three to six months for two years (31). In cases of incomplete excision or partial capsulectomy, adjuvant treatment should be discussed in a multidisciplinary team. In cases of capsule invasion, metastasis to regional lymph nodes, or systemic lymphoma involvement, curative-intent chemotherapy is recommended (31).

Lars Frich is an associate editor of the Journal of the Norwegian Medical Association and has not been involved in the editorial process for this article.

The article has been peer-reviewed.

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