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PRACTICE POINTER

Anaplastic large cell lymphoma in people with breast implants

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What you need to know

- Most cases of breast implant associated anaplastic lymphoma (BIA-ALCL) are indolent and present as unilateral breast swelling eight to 10 years after implant surgery, but symptoms can be non-specific and have been reported as early as three months after implant surgery
- Increasingly, evidence supports a causal relation between highly textured, high surface area implants and anaplastic large cell lymphoma
- Report all cases to the relevant national medicines regulatory authority

A woman in her 40s presents to her GP with painless unilateral breast swelling, eight years after unilateral mastectomy and implant based breast reconstruction. Clinical examination reveals an isolated uniform swelling of the breast only, with no palpable mass or lymphadenopathy. Ultrasonography confirms the presence of a homogenous effusion, and cytological evaluation of the effusion aspirate shows pleomorphic lymphocytes that are CD30 positive and anaplastic lymphoma kinase (ALK-1) negative.

The link between breast implants and systemic disease has been debated since the 1960s. Through the rise of patient advocacy and communication, largely via social media, an increasing number of women are attributing a variety of systemic symptoms to their implants.[1] The medical profession's response has been tardy, but it is starting to acknowledge that, through chronic immune activation, implants may result in allergies, autoimmune diseases, immune deficiencies, and lymphoma.[2]

The first reported case of breast implant associated anaplastic lymphoma (BIA-ALCL) was published in 1997.[3] The World Health Organization recognised BIA-ALCL as a provisional entity nine years later.[4] Practice recommendation updates from the World Consensus Conference on BIA-ALCL in 2022 suggest that BIA-ALCL is now categorised as an "uncommon" or "emerging" condition rather than a "rare" occurrence.[5]

This article outlines the risk factors, assessment, and management of breast implant associated anaplastic large cell lymphoma. The text refers throughout to care of women, although the article is also relevant to care of any individual with breast implants.

Breast implants (estimated to be present in 35 million people worldwide[6]) are prostheses filled with silicone gel or saline, with either smooth or textured outer shells. Implants are inserted in up to 81% of people who require breast reconstruction after breast cancer surgery.[7] They may also be inserted for symmetrisation or cosmetic breast augmentation, which is growing in popularity, as suggested by a review showing a 41% increase in the number of procedures between 2010 and 2017 in the US.[8]

Outcome data for breast implantation, particularly long term safety profiles, are limited because regulation and monitoring of medical devices and implants are less rigorous than for pharmaceuticals. Since 2004, 3576 safety alerts relating to medical devices have been issued in the UK,[9] with 1200 serious incidents linked to breast implants between 2015 and 2018.[9 10]

What is BIA-ALCL?

As part of the normal healing process, a capsule develops around all breast implants as the body detects a foreign object and attempts to isolate it within fibrous scar tissue. BIA-ALCL is a form of T cell non-Hodgkin's lymphoma that forms within this capsule in some people. Women with implants that have a high texture-to-surface area ratio of the outer shells are thought to be at highest risk.

BIA-ALCL is distinct from other breast lymphomas, which are most frequently diffuse large B cell lymphomas.[11] BIA-ALCL is characterised by a monoclonal population of large anaplastic cells that variably express T cell markers but are uniformly CD30-positive and ALK-1 negative.[11] In one retrospective observational study of 87 patients with BIA-ALCL, survival rates of 94% and 91% at three and five years, respectively, were reported.[12]

Pathogenesis is likely multifactorial, but bacterial biofilms driving chronic inflammation, shedding of implant microparticles, and host genetics have been implicated.[13] Implant bacterial colonisation resulting in antigenic stimulation, specifically T cell activation, may be relevant as chronic T cell activation is known to be associated with other malignancies.

How do patients present? (fig 1)

This is one of a series of occasional articles to help doctors prevent, diagnose, and respond to adverse drug reactions that may be serious if not recognised.
The article describes an adverse reaction that can occur in response to a medical device rather than a drug; however, advisers to the *Adverse drug reaction* series felt this was a suitable topic to cover.

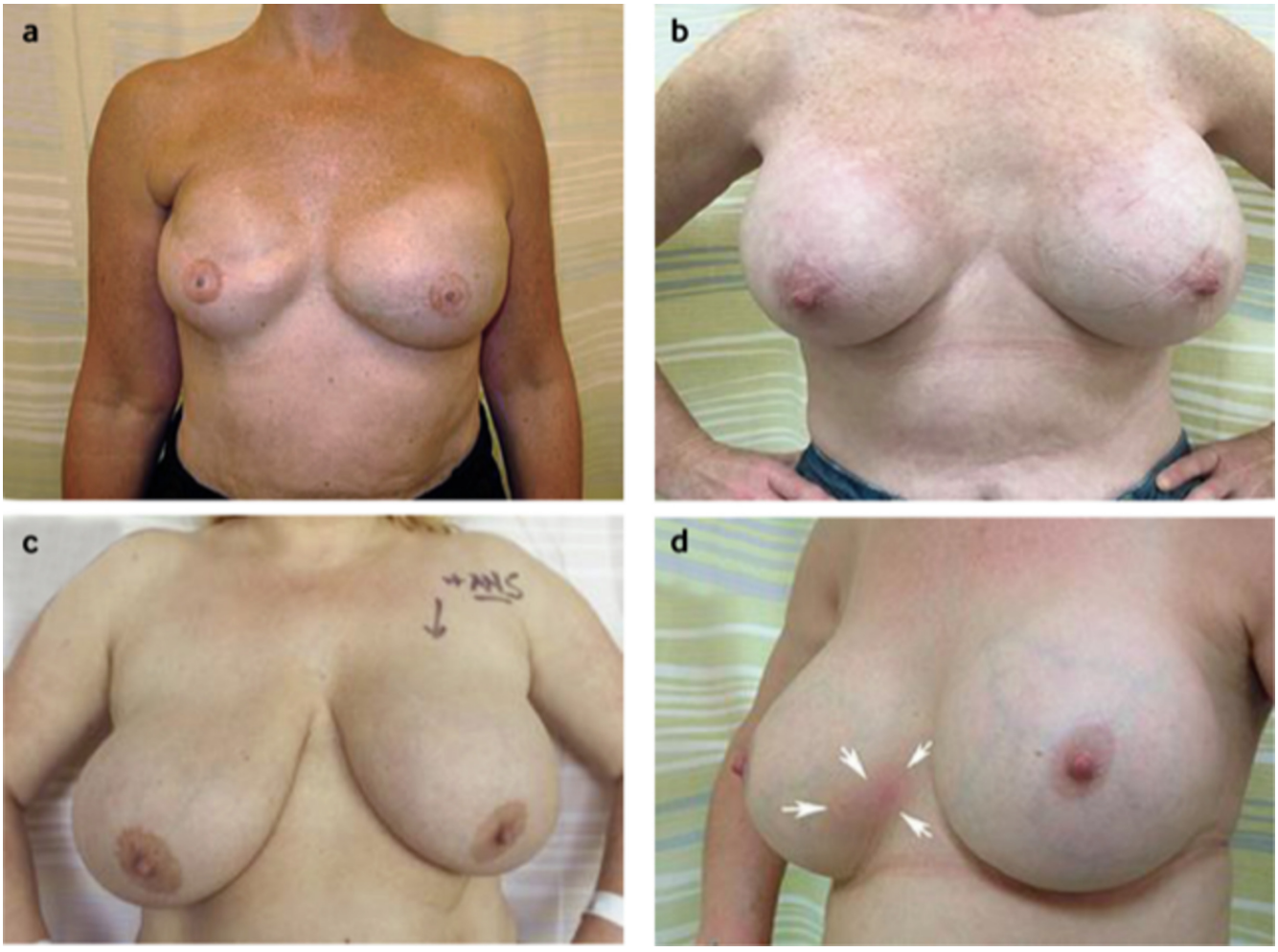

Fig 1 | Examples of clinical presentations of implant associated breast effusion caused by BIA-ALCL. (a) Effusion in a reconstructed left breast. (b) Effusion in an augmented left breast. (c) Subtle effusion in an augmented left breast; superior quadrant fullness is masked by underlying physiological asymmetry. (d) Rash of the lower inner quadrant of the right breast preceded the appearance of a BIA-ALCL mass at the same site (Reproduced with permission.[13] Patient consent obtained)

Around 80% of patients present with an effusion that causes painless breast swelling or asymmetry.[13 14] BIA-ALCL is indolent in most patients but can progress rapidly. If untreated, cells within seroma fluid can coalesce and acquire characteristics of solid tumours[11 15]; consequently, 15% of people with the condition have localised lymphadenopathy or distant disease on examination, or may report pain, masses, skin changes, and/or distortion of the implant or breast shape.[16 17] Approximately 9% present with "B symptoms" (night sweats, weight loss, and fevers).[18] Symptoms can be non-specific (eg, itching, increased breast firmness,[19] breast pain, erythema, implant distortion, night sweats, fevers, or weight loss), or may fluctuate in severity.[16]

Symptoms occur at a median of 8-10 years after implant insertion.[13] However, cases have been diagnosed within three months, or as late as 44 years following implantation.[20] In one case-control study of 43 patients with BIA-ALCL, 11 patients had a history of breast implants but no implant in situ at the time of diagnosis.[21]

How common is it?

As of April 2023,[22] 1363 patients in 48 countries have been diagnosed with BIA-ALCL, resulting in 59 deaths.[23] A marked increase in incidence occurred between 1990 and 2016, likely influenced by increased awareness and greater recognition in both medical and patient populations.[21] However, risk estimates rely on accurate recording of the prevalence of breast implantation, implant type, and true number of cases in a given population. Countries that have implemented specific informed consents, mandatory reporting of BIA-ALCL, and national prospective implant registries are associated with most tracked cases and therefore have a higher recorded prevalence.[24] In countries where these measures are not implemented, under-reporting, misdiagnosis, or missed diagnosis might also contribute to the lower prevalence.

What are the potential risk factors?

Textured outer shells

Shell texture is thought to reduce the risk of symptomatic capsular contraction and implant rotation. However, in 2021 the Scientific Committee on Health, Environmental, and Emerging Risks reported that after full literature search, evaluation of 605 publications, and public consultation with experts, a "moderate weight of evidence" suggested a causal relation between BIA-ALCL and textured implants.[25] According to several epidemiological studies and systematic reviews, this relation is relevant for all types of textured devices.[6 21 26 -28] However, the US Food and Drug Administration (FDA) has collated one of the largest data sets globally and linked most (84%, n=953) cases to a specific implant: BIOCELL,

manufactured by Allergan.[29] Silimed's polyurethane implants have also been implicated as high risk.[27] Both devices have now been withdrawn from use.[30-32] Other implant manufacturers that have been associated with BIA-ALCL are summarised in box 1. To date, only one case of BIA-ALCL has been recorded in a person with a smooth implant with no known history of textured implants—recorded in 2022 in the US.[29]

Box 1: Implant manufacturers that have been reported to be associated with cases of BIA-ALCL[33]

- Allergan Biocell implants were recalled in 2019[32 34 35]
- Silimed's CE certificate was suspended in Europe in 2015[30]
- Australia's Therapeutic Goods Administration has cancelled three breast implant entries from their register (Microthane, Micro Polyurethane, and Cristaline Paragel)[31]
- Mentor's imprinted Siltex Textured Breast Implants have exhibited a rare risk of BIA-ALCL (1:86 029 or 0.00001%)[27]
- Of 1130 unique BIA-ALCL cases reported as medical device reports to the FDA, 2% (n=20) are reported to have Sientra implants in situ and 1% (n=10) were listed as "other manufacturer" and included Bristol Myers Squib, Nagor, and Polytech[29]

The degree to which implant shells are textured varies according to implant type. Texturing is graded from 1 (smooth or "nano" textured) to 4 (highly or "macro" textured). Epidemiological studies have shown BIA-ALCL risk to be lower in implants with a lower texture-to-surface area ratio.[26 27] Table 1 summarises the risk estimates reported by various international organisations.

Table 1 | International estimates of BIA-ALCL risk and incidence

Source	Estimated risk/incidence of BIA-ALCL
Medicines and Healthcare products Regulatory Agency (UK)[33]	As of 31 December 2021, based on confirmed cases where surgery occurred in the UK: 1:16 500 implants sold
Health Canada[36]	Overall risk: 1:24 177 With Allergan implants: 1:3565 With Mentor implants: 1:16 703
Food and Drug Administration (US)[28]	Standardised incidence in the US ranges from 0.203 per 100 000 person-years to 31.1 per 100 000 person-years
Case-control study involving patients from the Dutch pathology registry[21]	Age adjusted incidence of BIA-ALCL from a textured device is 1:6920 at age 75
European Association of Plastic Surgeons Scientific Committee on Device Safety and Development[5 24]	As of 2022, based on 511 confirmed cases across 28 EU member states, prevalence reported as 1:11 297
Provisional data presented at the World BIA-ALCL Conference in 2022[23]	Risk estimation of developing BIA-ALCL specifically in Biocell implants may have increased in just three years from 1:3345[27] to 1:124[23]
American Association of Plastic Surgeons 2023 meeting. Podium presentation of prospective observational study data[37]	Cumulative incidence in cosmetic breast augmentation population 1:250. Allergan Biocell incidence 8.6 cases/1000 individuals Mentor Silitex incidence 1.3/1000
Collet et al review of global literature pertaining to BIA-ALCL[27]	This review identified "dramatic increases" in the incidence and risk of BIA-ALCL compared with initial estimates (1 per million versus 1:2832). However, it also highlighted barriers to the accurate estimation of proportion of women with implants and BIA-ALCL case numbers (poor registries, under-reporting, lack of awareness, cosmetic tourism, fear of litigation)

Longitudinal studies of BIA-ALCL diagnosed in Australasia between 2007 and 2019 found that all cases involved textured implants,[26 27] and 78.9% were related to highly textured implants (grade 3 or 4).[27] Furthermore, four devices (Mentor, Allergan, Nagor, and Silimed) comprised 87% of 143 implants used in patients with BIA-ALCL.[26] The risk of developing BIA-ALCL is estimated to be 16.5 times higher for Allergan Biocell (grade 3 textured) implants and 23.4 times higher with Silimed polyurethane (grade 4 textured) implants, compared with Silitex (grade 2 textured devices).[27]

Patient perspective

Very few people know about the FDA warnings or the recall of Allergan implants in 2019. We (the patients) would like to see all specialties informed, not just the plastic surgeons. As more and more women become symptomatic, they are likely to seek help from different physicians. But it is operating surgeons who need to notify their patients of the recall.

Roxane Vermeland, patient co-author and BIA-ALCL patient and advocate

Age

A case-control study in the Netherlands found cumulative risk increased with age, from 29 per million at age 50 to 82 per million at age 70.[21] Additionally, a systematic review involving 248 cases showed that patient age at first implantation was inversely associated with the length of time between insertion of breast implants and onset of BIA-ALCL symptoms; thus the authors of the review concluded older women may be more likely to develop BIA-ALCL sooner compared with younger women.[24]

Ethnicity and geography

Women who are white and of European ancestry may be more likely to develop BIA-ALCL. Only four cases of BIA-ALCL in women of Asian ancestry and one of African ancestry have been published in the literature.[26 38] However, the BIA-ALCL global network in October 2022 reported 12 cases in South East Asian countries, and four in African countries.[23] Nevertheless, most cases appear to be in people with European ancestry. Geographical variation was also noted in a 2018 summary of BIA-ALCL: 1:11 765 (255 cases) in the US, 1:6920 (40 cases) in the Netherlands, and 1:3345 (81 cases) in Australia[14] —this may reflect variations in implant types used globally or differences in data collection and reporting of cases.

Genetics

It is unclear if BIA-ALCL has a genetic link; however, a case series involving exome sequencing of 22 confirmed BIA-ALCL specimens

found relevant epigenetic alterations and cascade mutations in 74% and 60% of cases, respectively.[39]

Genetic predisposition to developing cancer may, at least in part, contribute to BIA-ALCL, as suggested by the higher incidence of BIA-ALCL observed in Li-Fraumeni syndrome[21] and carriers of the BRCA 1 or 2 or TP53 mutations.[5] In a 2020 study,[40] 15 cases of BIA-ALCL after breast reconstruction with silicone prostheses were identified using the Dutch national Pathology Database. Four patients were carriers of the BRCA 1 or 2 mutation, yielding an absolute risk of developing BIA-ALCL of 1:1551 in women aged 75 with BRCA 1 or 2 mutations, compared with a 1:7507 risk in women from the general population.[40]

How is it diagnosed?

Figure 2 offers an algorithm for the process of diagnosing BIA-ALCL.

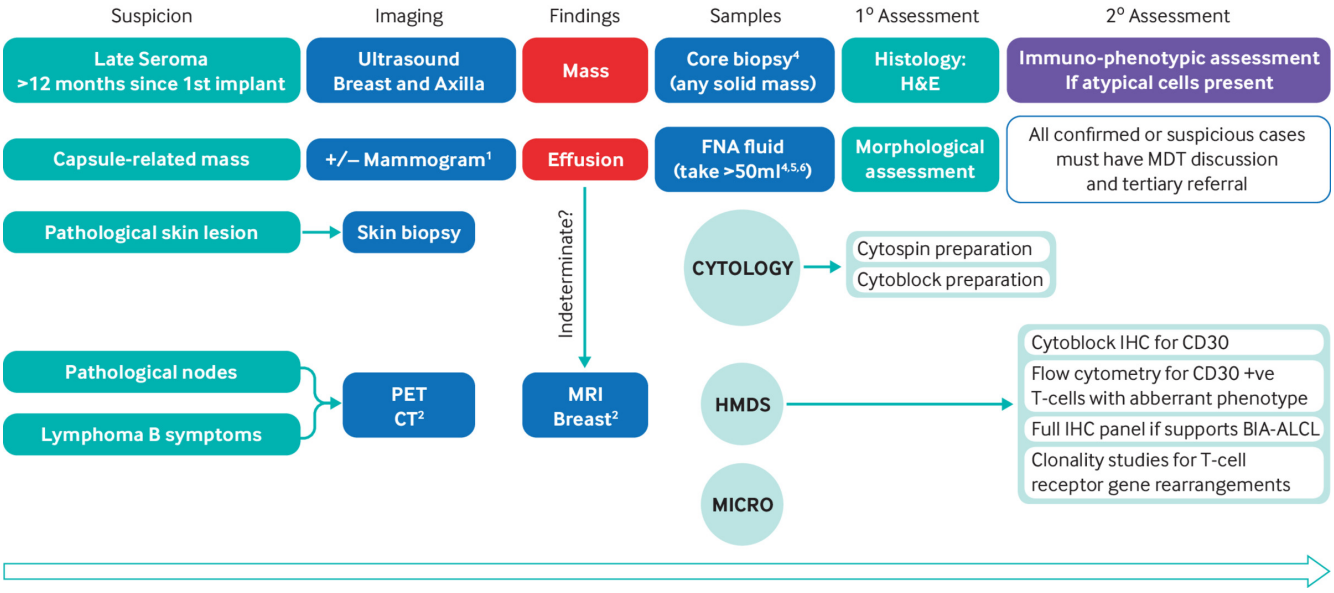

Fig 2 | Diagnostic algorithm used in the UK (adapted from the American NCCN Clinical Practice Guidelines) for assessment of new breast symptoms on the background of breast implants. 1) Mammogram if age >40: not useful for diagnosis of BIA-ALCL but to look for other pathology. 2) If lymphoma B symptoms and/or pathological nodes are present, request positron emission tomography/computed tomography (PET/CT) to investigate possible systemic disease, and consider diagnostic excision of the node. 3) Magnetic resonance imaging (MRI) if diagnosis is indeterminate or clarification is required. 4) Pathology requests should specifically state concern of BIA-ALCL. 5) Take maximum volume possible. Sample should be split: majority is for cytology. 6) Assessments 1 and 2 should be done on the same initial fluid take if possible (sometimes second or third collections can turn out falsely negative) FNA=fine needle aspiration; HMDS=haematological malignancy diagnostic service; IHC=immunohistochemistry; H&E=haematoxylin and eosin (stain). Reproduced with permission[13]

Diagnosis is typically based on clinical history, examination, and ultrasound, with sampling of the entirety of the peri-implant effusion to enable accurate cytological and immunohistochemical analysis of the peri-implant fluid (fig 2). A positive aspirate demonstrates pleomorphic lymphocytes that are characteristically ALK-1 negative and strongly CD30 positive. Sampling of lymph nodes, skin lesions, and masses may be required.

Cytological assessment for BIA-ALCL has a sensitivity of approximately 78%.[13] If there is ongoing suspicion of BIA-ALCL following negative cytology, multidisciplinary team (MDT) discussion and tertiary centre referral are recommended. Follow up patients with non-suspicious findings at three months to rule out progression or recurrence of symptoms.

How is it managed?

The National Institute for Health and Care Excellence recommends that all positive BIA-ALCL diagnoses are reviewed within a specialist integrated haematological malignancy diagnostic service.[41] All nations advocate an MDT approach under joint haemato-oncology and surgical care.[13 42 43] En-bloc resection (removing the implant and surrounding capsule as one) is the gold standard. Preoperative fluorodeoxyglucose PET/CT imaging is performed to stage local and distant disease and MRI may aid in diagnostic uncertainty or facilitate pre-operative planning.

In locally advanced or distant disease, systemic treatment may be indicated. Because of the small case numbers for advanced BIA-ALCL, the most effective chemotherapeutic regimen remains unclear and is extrapolated from evidence underpinning the management of other systemic ALK negative ALCL.[13 42 44]

Outcomes are excellent for most patients if detected early and managed with multidisciplinary input according to recognised guidelines.[13]

How can the risk of harm be minimised?

Macro-textured implants are no longer being used; however, many women still have them in situ.[45] No evidence exists to suggest that partial or total removal of the implant capsule in asymptomatic patients mitigates risk of BIA-ALCL.[46] Current advice from international medicines regulation authorities and national plastic surgery societies is not to explant these devices.[45 47 48] However, this continues to be a topic of debate. On a background of rising BIA-ALCL case numbers, a systematic review of 248 cases published in 2023 suggested a single implant exchange reduced expected BIA-ALCL cases numbers by 30%, and by nearly 65% in patients undergoing two exchanges.[24]

As well as withdrawing some devices from registries, the FDA and ANSM recommend surgeons switch to smooth implants while causative links continue to be established.[49 50] Australia's

Therapeutics Goods Administration has proposed suspension of textured implants, but several types are still available in Australia.[31] Other nations, including the UK, have shifted towards "nano" (grade 1) textured implants.

Practice recommendation updates from the World Consensus Conference on BIA-ALCL in 2022 included counselling women with BRCA 1 or 2 or TP53 mutations who are considering breast implants about the possible increased risk of BIA-ALCL.[5]

We advocate mandatory contribution to implant registries. Since 2019 patient consent is no longer required to submit implant details to the UK Breast and Cosmetic Implant Registry. Input is mandatory for NHS funded surgery but not private procedures. Similar registries exist throughout the world[51] to monitor trends and promptly identify device specific issues. Nevertheless, many adopt an "opt-in" approach whereby contribution is best practice rather than mandatory.

In 2020 an independent safety review of medicines and medical devices in the UK[52] highlighted systemic failures in listening to patient's concerns, identifying trends in practice and outcomes that give rise to safety concerns, and "glacial" movement when, belatedly, the healthcare sector decided to act.[52] Adopting approval processes that scrutinise pharmaceuticals safety could be applied to medical devices to offer reassurance to clinicians and patients and potentially reduce harm. Patients alleging harm from their breast implants must feel listened to in order to prevent the perpetuation of a "disjointed, siloed, unresponsive, and defensive" healthcare system.[52]

Some Australian health boards are notifying breast implant patients of their increased risk of BIA-ALCL and providing education. Other countries, including the UK, continue to debate whether a concerted public health campaign to increase awareness is appropriate.[45]

As symptoms of BIA-ALCL present at a median of 8-10 years following implantation,[13] it is too early to see the impacts following recall of certain implants. In fact, an increase in reported cases in the next 10 years is predicted as a result of the peak of high risk textured implant utilisation, as suggested by national market trends.[53]

Patient perspective

Patients aren't being informed about this cancer. It's frustrating to hear that they are going to their physicians and being told nothing is wrong. Why isn't anyone listening? We have hundreds of breast implant [social media] groups, one with almost 200 000 people. We, as patients, are helping other patients ... I had to create a "go fund me" page to attend the 1st World Conference on BIA-ALCL, because I didn't have that kind of money after being diagnosed and not working. I attended, by myself, and learnt how to treat my cancer. We need doctors to learn how to recognise the symptoms, and learn how to treat it. It's that easy.

Roxane Vermeland, patient co-author and BIA-ALCL patient and advocate

Case outcome

BIA-ALCL is diagnosed. The patient undergoes PET/CT imaging before surgical removal of the implant within the breast capsule (explantation with capsulectomy). Radiology and histology confirm that disease is localised to the capsule only.

Tips for people with breast implants

- Self-check breasts and armpits monthly for any new changes
- Keep all details of your breast implant/tissue expanders (manufacturer, model, date of insertion, any other removals/re-implantations)
- If you notice any new breast symptoms, seek advice from your implanting surgeon or hospital. If you cannot contact these, consult your GP
- If you experience unexpected weight loss, fever, or drenching night sweats, consult your GP
- If concerned about BIA-ALCL, your clinician will involve specialist diagnostic services including haematology and histopathology

Education into practice

- What support do you offer patients who have received implants, or who are considering them?
- When would you consider BIA-ALCL in a patient with breast implants?

How patients were involved in the creation of this article

Roxane Vermeland was diagnosed with stage 4 BIA-ALCL in 2018. Excerpts of her comments are included as boxes in the text. She has been involved in the development of this article, has helped to provide data from the most up-to-date sources, and has been involved in reviewing and editing of the final manuscript.

One external patient reviewer arranged by *The BMJ* highlighted additional literature that discussed alternative presentations of BIA-ALCL that were subsequently included.

Both patients highlighted the debate surrounding explantation of implants, and assisted with the wording of the article to improve clarity.

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The case in this article is fictitious and therefore no consent was required. Informed written consent was obtained from BIA-ALCL patient, coauthor, and patient advocate Roxane Vermeland for the inclusion of her opinions in this manuscript. Furthermore, she has reviewed and approved the final version of this manuscript for publication.

Contributorship statement and guarantor: All authors have reviewed and approved the final contents of the submission, have been actively involved in its production, and have consented to their inclusion. Further details of their contribution can be found below. The structure and general style instructions have been read and adhered to. No writing assistance was obtained.

C Brennan: Conceptualisation and project proposal, literature search, and data curation, writing: original draft, review, and editing.

A Moorhouse: Literature search and data curation, writing—original draft, review, and editing.

R Vermeland: Patient data input, review, and editing of original and final draft.

P Kneeshaw: Supervision, review, and editing of original and final drafts.

Provenance and peer review: commissioned, based on an idea from the author; externally peer reviewed.

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1 Magnusson MR, Cooter RD, Rakhorst H, McGuire PA, Adams WP, JrDeva AK. Breast implant illness: a way forward. *Plast Reconstr Surg* 2019;143(3S A Review of Breast Implant-Associated Anaplastic Large Cell Lymphoma):-81S. doi: 10.1097/PRS.0000000000005573 pmid: 30817559

2 Cohen Tervaert JW, Mohazab N, Redmond D, van Eeden C, Osman M. Breast implant illness: scientific evidence of its existence. *Expert Rev Clin Immunol* 2022;18:-29. doi: 10.1080/1744666X.2022.2010546 pmid: 34882509

3 Keech JA, JrCreech BJ. Anaplastic T-cell lymphoma in proximity to a saline-filled breast implant. *Plast Reconstr Surg* 1997;100:-5. doi: 10.1097/00006534-199708000-00065 pmid: 9252643

4 Swerdlow SH, Campo E, Pileri SA, et al. Review Series The updated WHO classification of hematological malignancies. The 2016 revision of the World Health Organization classification of lymphoid neoplasms.

5 Santanelli di Pompeo F, Clemens MW, Atlan M, etal. 2022 practice recommendation updates from the World Consensus Conference on BIA-ALCL. *Aesthet Surg J* 2022;42:-78. doi: 10.1093/asj/sjac133 pmid: 35639805

6 Collett DJ, Rakhorst H, Lennox P, Magnusson M, Cooter R, Deva AK. Current risk estimate of breast implant-associated anaplastic large cell lymphoma in textured breast implants. *Plast Reconstr Surg* 2019;143(3S A review of breast implant-associated anaplastic large cell lymphoma):-40S. doi: 10.1097/PRS.0000000000005567 pmid: 30817554

7 Broyles JM, Balk EM, Adam GP, etal. Implant-based versus autologous reconstruction after mastectomy for breast cancer: a systematic review and meta-analysis. *Plast Reconstr Surg Glob Open* 2022;10:e4180. doi: 10.1097/GOX.0000000000004180 pmid: 35291333

8 American Society of Plastics Surgeons, American Society of Plastic Surgeons. Plastic surgery statistics report, 2016. https://www.plasticsurgery.org/documents/News/Statistics/2017/plastic-surgery-statistics-full-report-2017.pdf

9 International consortium of investigative Journalists. International Medical Devices Database. The Implant Files. 2019. https://medicaldevices.icij.org/search?f%5Bcountry%5D=GBR&l=card&m=Device

10 Devlin H, Osborne H, Barr C. Breast implants study reveals serious safety concerns. *Guardian* 2018 Nov 26. https://www.theguardian.com/society/2018/nov/26/breast-implants-study-reveals-serious-safety-concerns

11 Jones JL, Hanby AM, Wells C, etalNational Co-ordinating Committee of Breast Pathology. Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL): an overview of presentation and pathogenesis and guidelines for pathological diagnosis and management. *Histopathology* 2019;75:-96. doi: 10.1111/his.13932 pmid: 31166611

12 Clemens MW, Medeiros LJ, Butler CE, etal. Complete surgical excision is essential for the management of patients with breast implant-associated anaplastic large-cell lymphoma. *J Clin Oncol* 2016;34:-8. doi: 10.1200/JCO.2015.63.3412 pmid: 26628470

13 Turton P, El-Sharkawi D, Lyburn I, etal. UK guidelines on the diagnosis and treatment of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) on behalf of the Medicines and Healthcare products Regulatory Agency (MHRA) Plastic, Reconstructive and Aesthetic Surgery Expert Advisory Group (PRASEAG). *J Plast Reconstr Aesthet Surg* 2021;74:-29. doi: 10.1016/j.bjps.2020.10.064 pmid: 33483089

14 Dixon JM, Clemens M. Breast implants and anaplastic large cell lymphoma. *BMJ* 2018;363:. doi: 10.1136/bmj.k5054 pmid: 30504242

15 Leberfinger AN, Behar BJ, Williams NC, etal. Breast implant-associated anaplastic large cell lymphoma. A systematic review. *JAMA Surg* 2017;152:-8. doi: 10.1001/jamasurg.2017.4026 pmid: 29049466

16 Quesada AE, Medeiros LJ, Clemens MW, Ferrufino-Schmidt MC, Pina-Oviedo S, Miranda RN. Breast implant-associated anaplastic large cell lymphoma: a review. *Mod Pathol* 2019;32:-88. doi: 10.1038/s41379-018-0134-3 pmid: 30206414

17 Jaffe ES, Ashar BS, Clemens MW, etal. Best practices guideline for the pathologic diagnosis of breast implant—associated anaplastic large-cell lymphoma. *J Clin Oncol* 2020;38:-11. doi: 10.1200/JCO.19.02778 pmid: 32045544

18 McCarthy CM, Loyo-Berríos N, Qureshi AA, etal. Patient registry and outcomes for breast implants and anaplastic large cell lymphoma etiology and epidemiology (PROFILE): initial report of findings 2012-2018. *Plast Reconstr Surg* 2019;143(3S A review of breast implant-associated anaplastic large cell lymphoma):-73S. doi: 10.1097/PRS.0000000000005571 pmid: 30817558

19 Fine KE, Wi M, Bennett DC. Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL): a collaborative effort for diagnosis and treatment. *Ann Breast Surg* 2019;3:doi: 10.21037/abs.2019.01.01.

20 Mehta-Shah N, Ghione P. An updated approach and understanding of breast implant-associated anaplastic large cell lymphoma. *J Natl Compr Canc Netw* 2022;20:-15. doi: 10.6004/jnccn.2022.7004 pmid: 35276670

21 de Boer M, van Leeuwen FE, Hauptmann M, etal. Breast implants and the risk of anaplastic large-cell lymphoma in the breast. *JAMA Oncol* 2018;4:-41. doi: 10.1001/jamaoncol.2017.4510 pmid: 29302687

22 Santinelli di Pompeo F. Personal communication. 2023.

23 Santanelli di Pompeo F. To explant or not to explant. https://www.youtube.com/watch?v=KfqoE_hD7A4

24 Santanelli Di Pompeo F, Panagiotakos D, Firmani G, Sorotos M. BIA-ALCL epidemiological findings from a retrospective study of 248 cases extracted from relevant case reports and series : a systematic review. *Aesthet Surg J* 2023;43:-55. doi: 10.1093/asj/sjac312 pmid: 36441968

25 De Jong WH, Panagiotakos D, Proykova A, etalSCHEER. Electronic address: sante-c2-scheer@ec.europa.euSCHEER. Final opinion on the safety of breast implants in relation to anaplastic large cell lymphoma: Report of the scientific committee on health, emerging and environmental risks (SCHEER). *Regul Toxicol Pharmacol* 2021;125:104982. doi: 10.1016/j.yrtph.2021.104982 pmid: 34214611

26 Loch-Wilkinson A, Beath KJ, Magnusson MR, etal. Breast implant-associated anaplastic large cell lymphoma in Australia: a longitudinal study of implant and other related risk factors. *Aesthet Surg J* 2020;40:-46. doi: 10.1093/asj/sjz333 pmid: 31738381

27 Magnusson M, Beath K, Cooter R, etal. The epidemiology of breast implant-associated anaplastic large cell lymphoma in Australia and New Zealand confirms the highest risk for grade 4 surface breast implants. *Plast Reconstr Surg* 2019;143:-92. doi: 10.1097/PRS.0000000000005500 pmid: 30789476

28 Lynch EB, DeCoster RC, Vyas KS, etal. Current risk of breast implant-associated anaplastic large cell lymphoma: a systematic review of epidemiological studies. *Ann Breast Surg* 2021;5:. doi: 10.21037/abs-20-96 pmid: 35415602

29 US Food and Drug Administration. Medical device reports of breast implant-associated anaplastic large cell lymphoma. https://www.fda.gov/medical-devices/breast-implants/medical-device-reports-breast-implant-associated-anaplastic-large-cell-lymphoma

30 Medicines and Healthcare products Regulatory Agency. Devices made by Silimed: Update from MHRA on the suspension of devices made by Silimed. https://www.gov.uk/government/publications/devices-made-by-silimed

31 Therapeutics Goods Administration. Breast implants and anaplastic large cell lymphoma. Update—suspended breast implant devices now cancelled. 2023. https://www.tga.gov.au/news/safety-alerts/breast-implants-and-anaplastic-large-cell-lymphoma

32 US Food and Drug Administration. Allergan voluntarily recalls BIOCELL. 2019. https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/allergan-voluntarily-recalls-biocellr-textured-breast-implants-and-tissue-expanders

33 Medicines and Healthcare products Regulatory Agency. Breast implant associated anaplastic large cell lymphoma (BIA-ALCL). https://www.gov.uk/guidance/breast-implants-and-anaplastic-large-cell-lymphoma-alcl#history

34 Depolo J. Allergan issues worldwide recall of Biocell textured breast implants and tissue expanders. 2023. https://www.breastcancer.org/research-news/allergen-recalls-biocell-textures-implants

35 US Food and Drug Administration. FDA takes action to protect patients from risk of certain textured breast implants; requests Allergan voluntarily recall certain breast implants and tissue expanders from market. https://www.fda.gov/news-events/press-announcements/fda-takes-action-protect-patients-risk-certain-textured-breast-implants-requests-allergan

36 Health Canada. Summary Safety Review—Breast implants—Assessing the potential risk of cancer (Breast implant associated anaplastic large cell lymphoma). 2023. https://hpr-rps.hres.ca/reg-content/summary-safety-review-detail.php?lang=en&linkID=SSR00223

37 Santanelli di Pompeo F, Kolasinski J, Sorotos M. Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL). Prevalence in a cohort of 1508 patients from a private cosmetic practice. *Plast Reconstr Surg Glob Open* 2023;11:. doi: 10.1097/01.GOX.0000934164.77429.33.

38 Wang Y, Zhang Q, Tan Y, etal. Current progress in breast implant-associated anaplastic large cell lymphoma. *Front Oncol* 2022;11:785887. doi: 10.3389/fonc.2021.785887 pmid: 35070989

39 Laurent C, Nicolae A, Laurent C, etal. Gene alterations in epigenetic modifiers and JAK-STAT signaling are frequent in breast implant-associated ALCL. *Blood* 2020;135:-70.pmid: 31774495

40 de Boer M, Hauptmann M, Hijmering NJ, etal. Increased prevalence of BRCA1/2 mutations in women with macrotextured breast implants and anaplastic large cell lymphoma of the breast. *Blood* 2020;136:-72. doi: 10.1182/blood.2019004498 pmid: 32452517

41 Snowden JA, O'Connell S, Hawkins J, etalGuideline Committee. Haematological cancers: improving outcomes. A summary of updated NICE service guidance in relation to Specialist Integrated Haematological Malignancy Diagnostic Services (SIHMDS). *J Clin Pathol* 2017;70:-8. doi: 10.1136/jclinpath-2016-204029 pmid: 28389440

42 Clemens MW, Jacobsen ED, Horwitz SM. 2019 NCCN consensus guidelines on the diagnosis and treatment of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL). *Aesthet Surg J* 2019;39(suppl_1):-13. doi: 10.1093/asj/sjy331 pmid: 30715173

43 Therapeutic Goods Administration (TGA). BIA-ALCL: Information for health professionals. BIA-ALCL: Information for health professionals | Therapeutic Goods Administration (TGA).

44 Horwitz S, O'Connor OA, Pro B, etalECHELON-2 Study Group. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. *Lancet* 2019;393:-40. doi: 10.1016/S0140-6736(18)32984-2 pmid: 30522922

45 Turton P, Johnson L, Macneill F. BIA-ALCL UK guidelines—an update. BAPRAS. https://clinicalaudit.hscic.gov.uk

46 Tanna N, Calobrace MB, Clemens MW, etal. Not all breast explants are equal: contemporary strategies in breast explantation surgery. *Plast Reconstr Surg* 2021;147:-18. doi: 10.1097/PRS.0000000000007784 pmid: 33776030

47 US Food and Drug Administration. Questions and answers about breast implant-associated anaplastic large cell lymphoma (BIA-ALCL).

48 Medicines and Healthcare products Regulatory Agency. MHRA statement on Allergan. https://www.gov.uk/government/news/mhra-statement-on-allergan

49 Vaysse C, Laurent C, Ysebaert L, Chantalat E, Chaput B. France: The first country to ban a type of breast implant linked to anaplastic large cell lymphoma. *Aesthet Surg J* 2019;39:-3. doi: 10.1093/asj/sjz142 pmid: 31152583

50 McCarthy M. Rare lymphoma is linked to breast implants, US officials conclude. *BMJ* 2017;356:. doi: 10.1136/bmj.j1507 pmid: 28336565

51 Implant Register. The Registry of Implant-Registries. https://implant-register.com/the-registry-of-implant-registries/

52 The Independent Medicines and Medical Devices Safety Review. The Cumberlege Report—oral hearings. https://www.immdsreview.org.uk/Report.html

53 Matros E, Shamsunder MG, Rubenstein RN, etal. Textured and smooth implant use reported in the tracking operations and outcomes for plastic surgeons database: epidemiologic implications for BIA-ALCL. *Plast Reconstr Surg Glob Open* 2021;9:e3499.pmid: 33758732