Medical Research Archives

ESMED
European Society of Medicine

OPEN ACCESS

Published: August 31, 2022

Citation: Reinhard R, Biermann N, et al., 2022. Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL), Medical Research Archives, [online] 10(8). https://doi.org/10.18103/mra.v10i8.2840

DOI
https://doi.org/10.18103/mra.v10i8.2840

ISSN: 2375-1924

REVIEW ARTICLE

Breast Implant Anaplastic Large Cell Lymphoma (BIA-ALCL): A Systematic Review and Case Report Regarding Incidence and Pathology Workup

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ABSTRACT

Background: Breast implant–associated anaplastic large cell lymphoma (BIA ALCL) is a rare indolent yet lethal disease. Recently the WHO accepted it as an individual new entity. Since then national and international registries have attempted to collect epidemiological data, but incidence rates vary strongly. The aim of this article is to provide an update on the status of the national BIA-ALCL registries and identify pitfalls alongside the current collection and diagnostic algorhythm.

Methods: A systematic review of the literature was performed and epidemiological data from national registries were compared. Furthermore a case report of a false positive diagnosis was added and the pitfalls alongside the diagnostic algorhythm was worked out.

Results: The comparison of national registries revealed significant differences in the collected data. Mean start of the registries was 2014, median 2015. Reporting of BIA-ALCL cases is mandatory except in two countries. Capture rates vary between 0-100%. Incidence rates range from 0.0 up to 8.9 per million implant years. The number of deaths does not correlate with the number of implants or the total population. The very same strains of CD30 can be interpreted differently.

Conclusion: Comparing epidemiologic data revealed significant differences among national registries. In particular, non-published sales data of breast implants and non-mandatory recording of the disease lead to an overall underreporting of cases. Therefore, the incidence rates still cannot be compared uniformly. Furthermore the definition of CD30 straining intensity should be standardized and adjusted in the guidelines.

Introduction

BIA-ALCL is a rare type of Non-Hodgkin Lymphoma (NHL) which is associated with mostly texturized breast implants[1].

Incidents are on the rise and even though it is still a rare disease with 733 reported and approximately 993 cases in total, it is expected to increase even further [2] [3] [4] [5].

In 1997, it was first suggested that there might be a link between breast implants and a new form of T-cell lymphoma[6]. Since only single cases were known, it was initially difficult to understand the pathogenesis and to derive therapeutic recommendations. This changed with first cohort studies[7] that provided epidemiologic information, revealed risk factors, and improved recommendations in suspect cases.

Hence in 2011, the FDA issued a safety communication warning of increasing evidence linking implants to a new form of ALCL[8]. Subsequently some national breast implant registries were established e.g. the swedish Bröstimplantatregistret[9].

It has been the subject of repeated discussion, particularly since its recognition as a separate entity by the WHO in 2016[10]. Since then, the number of annually reported cases has increased significantly. This eventually led to the possibility of more precise diagnostic and therapeutic recommendations of this rare, indolent yet lethal disease[11]. Today an interdisciplinary approach with early, specific detection proved to be associated with an excellent prognosis[12]. The diagnostic pathway now consists of clinical presentation, medical imaging, and pathologic workup[13]. In most cases a T-cell typical surface pattern was found and CD30 was consistently strong positive, with negative testing for ALK [14].

Despite these diagnostic improvements, the notification algorithm and follow-up after breast implant placement within registries is inconsistent. Non-mandatory reporting and opt-out regulations lead to an underreporting and unreleased sales data of breast implants impede the calculation of an exact incidence of the BIA-ALCL. Additionally, non-standardized immunohistochemical staining analysis may lead to false negative results.

To underline the importance of breast implant registries and outline the diagnostic workup, we systematically reviewed the literature and present a case report regarding the immunohistochemical staining process.

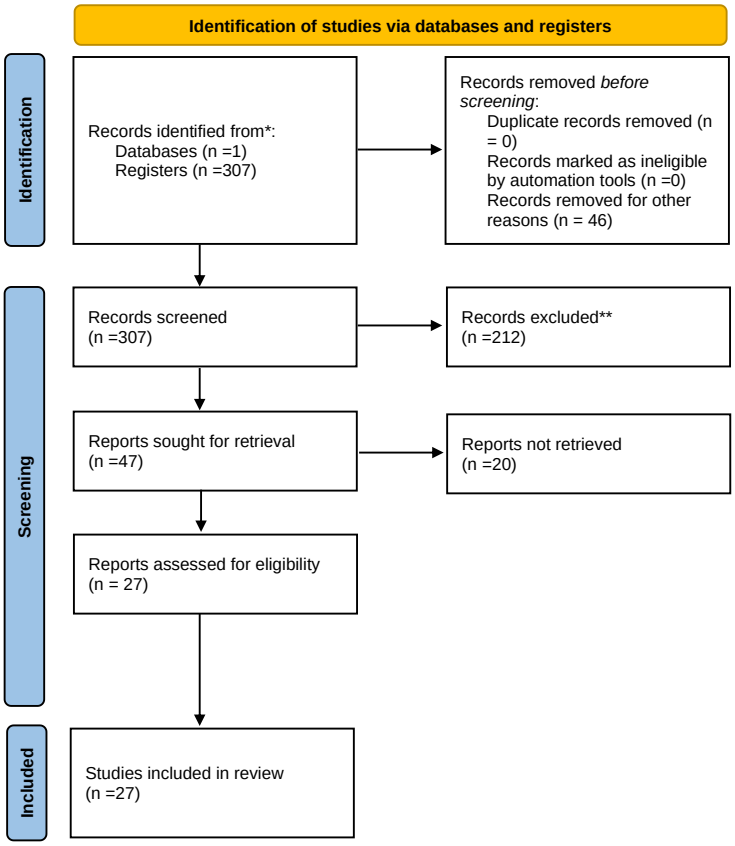

Figure 1 PRISMA 2020[15]

Country	Breast implant registry	Breast Augmentation in Public practice	Breast Augmentation in Privat practice	Registry start	Registry madatory	Report of BIA ALCL cases mandatory	BIA ALCL cases Total	BIA ALCL Deaths	Breast augmentation/ Year ISAPS	Total population	Incidence per 1.000.000 implant years
Australia	Australian Breast Device Registry	75 - 100%[16]	75 - 100%[16]	2014[16]	opt out[17]	No[18]	112[17]	4[19]	17 553[20]	25 877 751[21]	
Denmark	Danish Registry for Plastic Surgery	100%[16]	50 - 70%[16]	1999[16]	No[16]	Yes[22]	9[22]	0[22]	N.A.	5 873 420[23]	
France	French breast implant registry	25 - 50%[16]	0 - 25%[16]	2018[16]	N.A.	Yes[22]	86[22]	4[22]	53 938[24]	67 827 000[25]	
Germany	Implantat register Deutschland	N.A.	N.A.	2024[16]	Mandatory[16]	Yes[22]	30[26]	0[22]	67 634[27]	83 222 442[28]	East Bavaria: 0.0[29]
Italy	National Breast Implants Registry	0 - 25%[16]	0 - 25%[16]	2017[16]	No[16]	Yes[22]	79[30]	2[30]	39 276[27]	58 983 122[31]	3.5[32]
Netherlands	Dutch National Breast Implant Registry	100%[16]	94%[16]	2015[16]	opt out[16]	Yes[22]	65[22]	2[22]	N.A.	17 618 135[33]	8.9[34,29]
Spain	Sistema de Registro Espaniol de Implantes da Mama	0 - 25%[16]	0 - 25%[16]	2013[16]	opt out[16]	Yes[22]	40[22]	1[22]	44 406[27]	47 385 107[35]	
Sweden	Bröst implantat registret of Sweden	100%[16]	85%[16]	2014[16]	opt out[16]	Yes[22]	8[36]	2[22]	1 908[27]	10 379 295[37]	
United Kingdom	Breast and Cosmetic Implant Registry	75 - 100%[16]	50 - 75%[16]	2016[16]	opt out[16]	Yes[22]	83[38]	1[22]	36 930[24]	67 081 000[39]	
United States of America	National Breast Implant Registry	N.A.	0 – 25%[16]	2018[16]	opt out[16]	No	384[22]	12[40]	371 997[27]	331 893 745[41]	2.03[42,29] 1.7 – 2.5[42,29] 14.6[29,7] 45.1[29,43]

Table 1 Overview of breast implant Registries

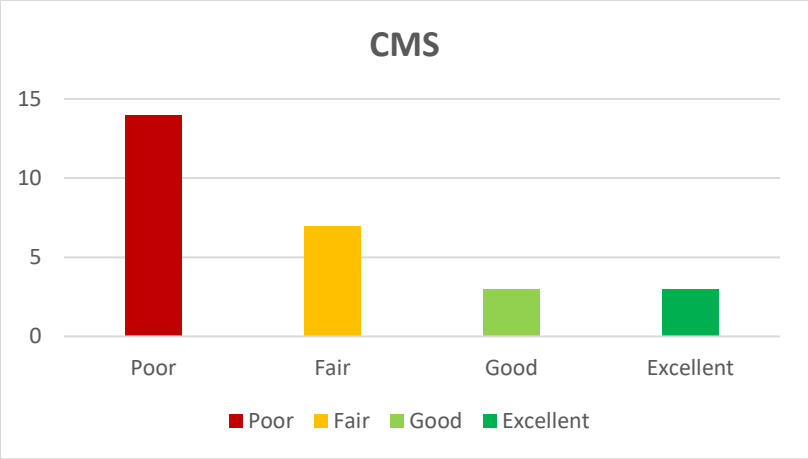

Table 2 Coleman Methodology Score

Material and Methods

The literature research was conducted according to the principles of Evidence-Based Practice (EBP) in a sequential approach. Guidelines of national and international standard were discovered searching the databases of the "Guidelines International Network[44]" and National Guideline Clearinghouse[45].

A systematic review of the literature was then conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[46]. The databases of PubMed has been comprehensively searched for meta-analysis, systematic or narrative reviews and primary clinical studies. The search interval included data until 28.02.2022 using various connections of the keywords “ALCL*” in combination with either "incidence"[All Fields] AND "breast"[All Fields] AND “implant”[All Fields].

Articles published in other languages than English or German have been excluded, yielding 306 relevant studies. Subsequent primary screening included the title and abstract of each manuscript. Studies without an abstract were excluded and the full text was obtained if the abstract did not allow finding the defined inclusion or exclusion criteria. Strict care was taken to consider only epidemiological studies. Studies primarily investigating the clinical diagnosis and operative procedure were excluded.

To reduce selection bias the abstracts to all articles were read and reviewed independently by the authors. According to their relevance the whole article was close read and subsequently assessed for eligibility and excluded respectively.
To define the quality of the studies, the Coleman Methodology Score (CMS) was utilized to all original articles. It assesses the scientific quality using 10 criteria, giving a total score ranging between 0 and 100 points. With 100 indicating a small chance for various biases and confounding factors. The final score can be defined as excellent (85 to 100 points), good (70 to 84 points), fair (50 to 69 points), and poor (< 50 points).

Results

Out of 307 studies, 306 clinical studies have been included. 212 studies have been excluded according to the screening process and 47 full-text articles were assessed for eligibility. Subsequently, 20 studies have been excluded after full-text analysis due to the exclusion criteria (Fig.1).
We found 27 clinical studies and reviews describing the incidence and notification requirements or algorithm of the BIA-ALCL (Fig.1).
Clinical evidence ranged from level II-IV according to the Oxford Centre for Evidence-Based Medicine. According to the CMS scoring system 14 studies revealed a poor, 7 studies a fair, 3 studies a good and 3 an excellent methodology.
Table 1 is an overview of the current breast implant registries. The mean start of the registries was 2014, the median 2015. According to Bargon et al. seven out of ten countries have a better registration coverage for public hospitals than in private clinics [16]. Six of nine countries claim up to 100% registration coverage for the public sector, in comparison to only three of ten countries with a private clinic coverage of over 90% (Tab.1).
At the time of publication, the German breast implant registry is not yet online. Starting in 2024, it is expected to be the first mandatory registry for public and private hospitals. Thus, a national 100% coverage rate for private and public clinics is to be achieved. Patients, clinics and health insurance companies are obligated to report to the database. Until now reporting rates of all countrys and registries vary and in most cases funding of the registries is not sustainable secured.
Worldwide, 36 people have died from BIA-ALCL to date[40]. The number of deaths does not correlate with the number of implantations. For example, four people died from BIA-ALCL in both Australia and France, while three times as many breast implants were implanted in France.
There is also no correlation between the implantation rate and the detected cases. Comparing Spain and Italy with similar annual implantation rates, almost twice as many cases were found in Italy.
There are also differences in the countries that have not yet suffered any deaths. Neither in Germany nor in Denmark, a fatal case has been reported with 30 and nine eoverall cases overall cases respectively.
Incidence rates range from 0.0 per million implant years in Germany up to 8.9 in the Netherlands.

Case Presentation

A 44-year-old woman carrying the BRCA-2 mutation, underwent total mastectomy and immediate reconstruction with texturized implants (MENTOR 375cc texturized CPG 322 Gel Breast). Postoperative she developed a seroma on the right side and got revised (MENTOR Cohesive III 375cc medium light-moderate plus profile).
One year past surgery a control MRI detected a seroma surrounding her left implant. The fluid with signs of chronic inflammation in the cytological examination was drained repeatedly for another year, when she finally decided to change both implants for a new smooth variant (MENTOR Cohesive I 350cc smooth round submuscular). Postoperative, pathology analysis of both capsules showed a complete resected BIA-ALCL infiltration on the right side. Further radiologic examinations were made but found no additional signs of malignancy. Therefore, a consensus conference recommended no further therapy. Uncertain whether this was correct, she decided to get a second opinion.
She was presented to us one-month past surgery with increasing pain in both breasts, axilla, and back, as well as long-lasting retrosternal pressure. The implants showed medial rippling and lateral movability on light pressure. The radiologic imaging was re-evaluated and additional CEUS-sonography and PET was taken. Increased lymph nodes and 3° capsular fibrosis, as well as capsule residues and a seroma surrounding both implants were found in the MRI scan.
According to current guidelines [47], we removed the implants, performed en-bloc capsulectomy [48], and resected the suspect lymph nodes. Pathology evaluation of the specimens showed activated medium sized, mildly CD30 positive and ALK-1 negative cells, but no typical signs of malignancy such as CD30 positive blast clusters.
For reference, the initial positive probes were reevaluated by two additional, independent pathology institutes. This time however, the

histological description as well as the diagnosis were not confirmed, as the CD30 intensity was described as lightly expressed. So according to international recommendations[49] further analyzations were made. Including the determination of T-cell-clonality by using multiplex-PCR and TCR-gamma/beta-receptor rearrangement analysis. Additional markers such as negative Ki67 and similar activity of CD3 to CD5 in activated T-cells were found confirming the rejection of the initial BIA-ALCL diagnosis [50].

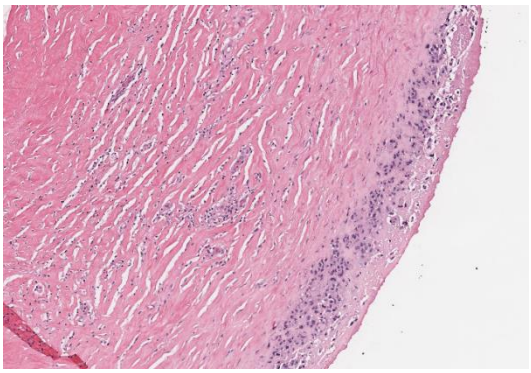

Figure 2

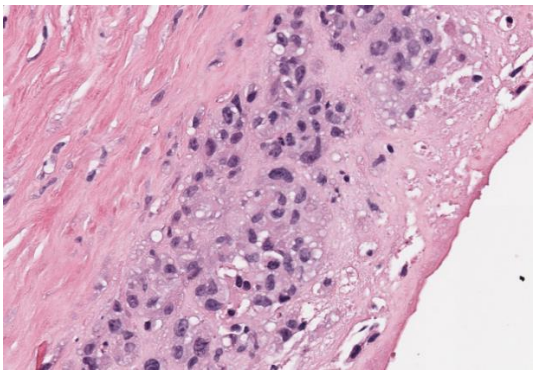

Figure 3

Fig. 1 and 2: pathology typical case of a BIA-ALC.
Haematoxylin and eosin (H&E) stain of a capsule biopsy with clearly discernible atypical blast, some of them with characteristic horse-shoe shaped nuclei (hallmark cells)
(courtesy of Prof. G. Ott, Departent of Clinical Pathology, Robert-Bosch-Krankenhaus, Stuttgart).

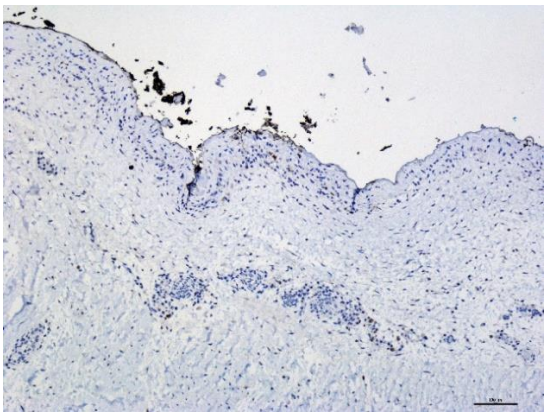

Figure 3

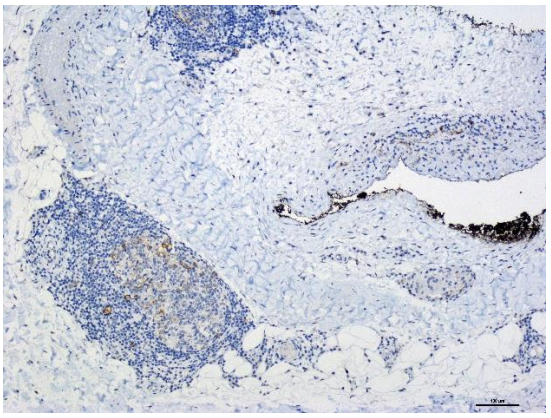

Figure 4

Figure 3-4 Two pictures of our case.
Low intensity, single spread CD30 pattern but no signs of lymphoid blasts.
Figure 4 Immunohistochemistry of a light positive but dense area of CD30. Typical pattern of CD30 positive blasts in lymph follicles (provided with the kind support of Dr. Utpatel, Department of Clinical Pathology, University Hospital Regensburg)

Discussion

We systematically reviewed the literature up on the incidence of BIA-ALCL through breast implant registries and outlined the importance of a standardized pathology workup with a case report. We found that the incidence strongly varies and the calculation itself is challenging. This is due to the varying transmission rates, on the other due to the heterogeneity of the collected units e.g. person and implant years. Additionally, unreleased sales data of breast implants account this mathematical uncertainty. Furthermore, the reporting rates of breast implant placement through breast implant registries yielded between 0% and 100% in public and private practices, respectively[16]. The reason for this heterogeneity lies within the political setting of these registries as most countries use opt-out systems leaving the reporting option to the surgeon. Even in Sweden with a 100% reporting rates in public and

85% in private clinics, the registered implants reach only 65%, possibly due to the higher number of breast augmentations in private clinics[36]. A similar situation is found in the United Kingdom, were up to 100% of the implants are registered in the public sector but an estimated of only 55% of all implants are thereby captured[51].

Again, the high number of breast augmentations in private clinics possibly accounts for the missing data considering the opt-out policy. Amongst other reasons this leads to an underreporting of cases as a comparison of the countries exemplifies. Australia reported a total of 112 cases over 25 million inhabitants[52], while the United States found only 384 cases with 330 million inhabitants[38], depicting a strong percental difference. Consequently standardized and legal binding registries will be the only way to acquire international comparable data[53] and contribute to the pathophysiology including genetic predisposition and implant surface texture [48,54].

Another reinforcing factor for underreporting and low numbers of BIA-ALCL are uncertainties within the pathological work up. As our case report offers a clear view on the diagnostic pathway and pitfalls alongside. Mistakes can already occur in the collection of the samples, obtaining the cytology, or taking the capsule tissue. According to the 2019 NCCN Consensus Guidelines on the Diagnosis and Treatment of BIA - ALCL [55] the diagnostic algorhythm consists of four stages. Detection of suspect symptoms, clinical imaging, biopsy and pathological workup.

Clinically, there is usually a unilateral or bilateral seroma, occurring between one and ten years after implantation [42]. Ultrasound or MRI is used to detect solid or fluid forms of the disease. Finally, biopsy or fineneedle aspiration of the fluid or tissue is performed followed by the pathological workup. There is still no recommendation on where and how many samples should be taken and wether and how much of the capsule should be excised. The following histological workup includes cytology, flow cytometry of T-cell clones and immunohistochemistry of CD30 [56] and further differentiation markers [57]. Especially the absence of ALK should be mentioned. CD30 positivity and ALK negativity alone are not sufficient for the diagnosis. Cluster differentiation and the experience of a hematopathologist is necessary. [57,55].

As described above the CD30 intensity of the very same paraffin blocks was interpreted differently by two independent pathological institutes. This led to two diametrically different diagnosis.

Consequently the question should be raised of whether the CD30 intensity could be quantified and standardized objectively[58]. Lymphoma supporting results have so far been described as highly intense [59], [60] in contrast to the light to moderate description in this case. Taking the density of CD30 during chronic infections into account, a distinction between infection and lymphoma might be possible.

Conclusion

The BIA-ALCL is a rare disease whose incidence is difficult to collect reliably. Unreleased sales data of breast implants, non-mandatory reporting to public health departments and opt-out regulations for breast implant registries lead to an underreporting of cases. Furthermore, this article should raise awareness to the importance over the interpretation of CD30 intensity as the current definition leaves room for false-positive results. The primary analysis will be morphological, and we strongly recommend that cytopathologists or breast pathologists who may initially receive such specimens work closely with hematopathology colleagues in large centres with high experience.

Conflict of interest

The authors have no conflicts of interest to declare.

The authors did not receive funding for this article.

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