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Anaplastic large cell lymphoma and breast implants: systematic review of published cases

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Abstract

Background and objective. In 1995, the first notification relating anaplastic large cell lymphoma (BIA-ALCL) and breast implants was established. Twenty four years later, hundreds of articles have been published about this topic.

The aim of this study is to review the published cases and summarize the current knowledge about this entity bringing it closer to Hispanic readers.

Methods. A systematic review was performed in PubMed, ScienceDirect, SciELO and Google Scholar databases since 1995 to October 2019.

Results. A total number of 122 case reports were analyzed. The information collected was heterogeneous. The shortage of Ibero-Latinoamerican published cases was evidenced. Data elements abstracted included information about patient demographics, medical history, implant characteristics, presenting symptoms, diagnosis and staging, treatment, and patient outcomes.

Conclusions. Despite diagnosis and current treatment to BIA-ALCL are fairly standardized, more rigorous studies are required to establish actual incidence and etiology. The lack of common criteria when collecting or reporting clinical cases makes difficult a truthful and uniform data collection. Communication of any incident related to breast implants, both to the national implant registries and to the scientific community, is necessary in order to gather quality information as a basis for evidence-based decision making.

Key words	Breast implant associated anaplastic lymphoma, Breast implants, Breast prosthesis.
Level of evidence	3b Therapeutic
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Introduction

Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is an uncommon subtype of T-cell non-Hodgkin lymphoma, developed in the scar tissue and fluid surrounding the implant and is usually successfully treated with prompt removal of the implant and surrounding scar capsule. Attention to this disease has grown considerably in the last few years.

In 1995[1] a case series presenting 3 women with cutaneous T-cell lymphoma associated to breast implants was published for the first time. In 1997, Keech and Creech[2] described the first case of BIA-ALCL in a patient with McGhan™ Style (Allergan plc. Dublin, Ireland) textured breast implants. In 2010, Brody G. presented for the first time 34 cases of BIA-ALCL at the American Society of Plastic Surgery Annual Meeting.[3] This communication caught the attention of the press and in 2011, the *Food and Drug Administration* from the United States (FDA) advised about the possible association between breast implants and the development of ALCL.[4] In June of the same year the first written work was published; it gathered information about 36 cases and maintained the focus on the subject.[5] From that moment, more and more cases of BIA-ALCL have been reported and in 2015, Brody G. et al made a publication in which 173 cases were presented, and the level of alarm was raised.[6]

In 2016, the World Health Organization (WHO) classified BIA-ALCL as a provisional new entity of anaplastic large cell lymphoma, distinct from other ALK negative lymphomas. The *National Comprehensive Cancer Network (NCCN)* established the first evidence-based clinical practice guidelines for diagnosis and treatment of the disease.[7] During this time, the number of papers about this subject has grown exponentially, and that resulted in a considerable improvement of knowledge about this lymphoma. Simultaneously, public alarm has grown, and that means professionals should try to provide accurate, updated and consensual information about BIA-ALCL.

BIA-ALCL incidence is estimated between 1/2832 and 1/30000 patients with breast implants,[8] although real incidence remains unknown. One of the main problems to calculate the real risk of developing BIA-ALCL is the lack of international breast implant registries.[9] The exact number of patients carrying breast implants is based on estimations, so determining the real incidence of the disease globally is a complicated task. Despite the establishment in the last few years of registries such as PROFILE (*Patient Registry and Outcomes For breast Implants anaplastic large cell Lymphoma etiology and Epidemiology*) and the specialists' awareness on the importance of diagnosing and notifying the disease, information collected is often deficient and inexact.

Nevertheless, the FDA issued a report in July 2019[10] with global information about the behavior of this lymphoma, from which it was revealed that the number of deaths worldwide amounts to 33 and that the disease is mainly related to the use of Allergan™ textured breast implants (including McGhan™ and Inamed™), both for aesthetic or reconstructive reasons.

The objective of the present study is to perform a systematic review of the published cases of BIA-ALCL and to synthetize the updated knowledge about this entity. To our knowledge, this is the first systematic review about this subject published in Spanish, as well as English, and it could help bring the knowledge about this lymphoma to the greatest possible number of professionals involved in its diagnosis and treatment.

Methods

A systematic review was performed according to PRISMA statement[11] (Preferred Reporting Items for Systematic review and Meta-Analysis). Literature research was conducted using PubMed, ScienceDirect and SciELO, aiming to identify every case of BIA-ALCL published so far (end of October 2019).

In PubMed, research was carried out using the following keywords: BIA-ALCL [Title/Abstract], implant associated anaplastic large cell lymphoma [Title/Abstract], "Breast implants" [Title] AND "lymphoma" [Title], ("breast implants"[MeSH Terms] OR ("breast"[All Fields] AND "implants"[All Fields]) OR "breast implants"[All Fields]) AND ("lymphoma"[MeSH Terms] OR "lymphoma"[All Fields]).

In ScienceDirect, we performed an advanced search (title, abstract, keywords) using the following keywords: BIA-ALCL, implant associated anaplastic large cell lymphoma, breast implants AND lymphoma, implants AND lymphoma.

In SciELO, an advanced search was also accomplished (Spanish and English, all indexes) including the next keywords: "*linfoma anaplásico de células gigantes asociado implantes, LACG, implantes mamarios AND linfoma, implantes AND linfoma*" (in Spanish).

Research was completed using Google Scholar, allowing the access to those documents known as "gray literature". An advanced search was carried out (*allintitle*) in English and Spanish, including the following terms: breast implant associated anaplastic large cell lymphoma, "breast implants" AND "lymphoma", "implants" AND "lymphoma, BIA-ALCL.

All the original articles, case notifications, revisions and clinical guidelines published, without any time period limit, were included. We included studies written both in Spanish and English. Those works in a different language, as well as letters to the editor, proceedings of conferences, books or comments were excluded, except from those cases obtained by indirect references, giving value and content to the description of the facts.

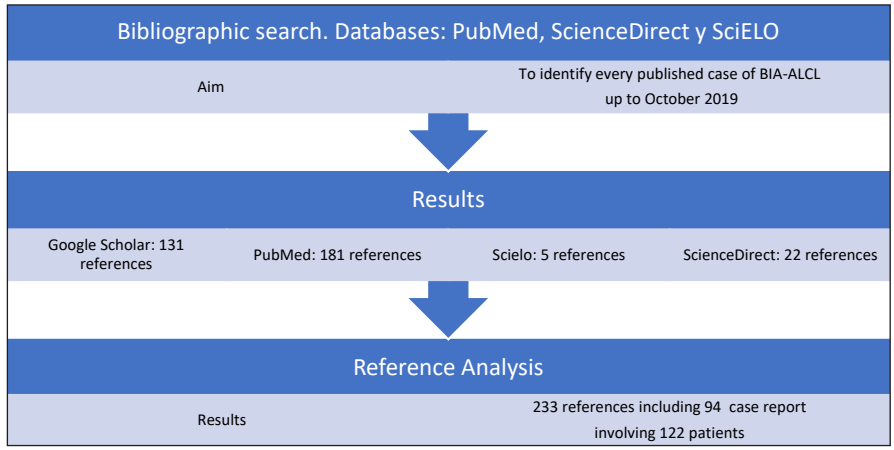

Figure 1. Flow chart. Article retrieval

After applying inclusion/exclusion criteria, 131 references were chosen from Google Scholar, 181 from PubMed, 5 from SciELO and 22 from ScienceDirect. Once duplicated references were merged and/or eliminated, we finally evaluated a total of 233 articles, including 94 case notifications (122 patients) (Fig. 1).

It should be emphasized that in 2015[6] a systematic review was published, including 173 cases of BIA-ALCL. However, only 79 of them were collected from published literature, while the remaining 94 cases were unpublished data, provided by different countries. This way we can justify the number of 122 cases included in this revision, taking in account that all of them come from cases published in the literature so far.

Results

A total number of 122 case reports were analyzed after applying the inclusion and exclusion criteria. During the review, the erratic report of the data without systematization or unified criteria was verified.

118 (97%) patients were women and 4 (3%) men by birth. The average age of patients documented was 51,89 years (24 to 87 years). The average time to disease presentation was 10.2 years (2 to 40 years).

23 (19%) cases were described as White, Caucasian or European; 4 (3%) Latin cases were described, 1 African American case, while in 94 (77%) cases this data was not reported. The cases came from the following countries: US 48 (39%), United Kingdom 11 (9%), Spain 11 (9%), Italy 10 (8.5%), Australia 9 (7%), New Zealand 7 (6%), Israel 5 (4%), Belgium 3, Brazil 3, Poland 2, Germany 2, Canada 2, Iran 2, Switzerland 1, Czech Republic 1, Greece 1, France 1, Holland 1, Mexico 1 and Denmark 1 (Table I,II).

The surgical indication was cosmetic in 64 (52%) of the patients, reconstructive in 47 (38%), gender confirmation in 4 (3%) and unknown in 7 (6%). One patient underwent breast implant augmentation for cosmetic reasons and subsequently developed breast cancer and mastectomy and implant reconstruction was indicated. The surgical plane used was: submuscular 37 (30%), subglandular 14 (11%), subfascial 1 (1%) and unknown 70 (57%). The affected breast was left 56 (46%), right 52 (43%), bilateral 3 (2.5%) and unknown in 11 (9%) cases.

Regarding medical record, 47 patients (38.53%) suffered from breast cancer (2 of them were BRCA mutation carriers), 4 patients (3.29%) had undergone gender reassignment treatment, 19 patients (15.57%) had a medical record without interest for the present study, 5 patients (4.1%) suffered from cancer other than breast cancer (we found 2 cases of Li Fraumeni syndrome), and in 47 cases (38.53%) no history was described.

Table I. Published cases distributed by country

Country	Number of cases
USA	48
UK	11
Spain	11
Italy	10
Australia	9
New Zealand	7
Israel	5
Belgium	3
Brazil	3
Iran	2
Germany	2
Poland	2
Canada	2
Czech Republic	1
Netherlands	1
Switzerland	1
Denmark	1
Greece	1
France	1
Mexico	1

Table II. Demographic data

	Number of patients	%
Age		
20 – 29 yo	1	0.81
30 – 39 yo	18	14.75
40 – 49 yo	35	28.68
50 – 59 yo	37	30.33
60- 69 yo	16	13.11
70 – 79 yo	10	8.20
80 – 89 yo	1	0.81
Unknown	4	3.28
Ethnics		
Caucasian	23	18.85
Latin	4	3.28
African	1	0.81
Unnown	94	77.05
Sex at birth		
Female	118	96.72
Male	4	3.28

Symptoms and clinical presentation

Increase in breast size, sometimes also referred to as "inflammation" was the most frequent clinical presentation and it was described in 102 patients (83.61%). A mass palpation, in isolation or accompanied by other symptoms, was detected in 19 patients (15.57%). The detection of suspicious axillary lymphadenopathies present at the time of diagnosis (13 patients, 10.66%) and the presence of B symptoms (6 patients, 4.92%) was also noted. In 5 cases (4.1%) the patients remained asymptomatic, and the detection of ALCL was an incidental finding. The authors did not describe the form of presentation in 4 cases (3.29%).

The increase in breast size occurred in 99 cases (81.15%) due to the presence of periprosthetic seroma. In 22 cases (18.03%) no seroma was demonstrated, and in 1 case (0.82%) no information was provided (Table III).

Supplementary tests

Breast ultrasound was performed in most cases due to the suspected diagnosis of ALCL. It was performed in isolation in 23 cases (18.85%), supplemented with mammography in 20 cases (16.39%), with MRI in 24 cases (19.67%), with mammography and MRI in 9 cases (7.38%), with mammography and CT in 4 cases (3.29%). Mammography alone was performed in 3 cases (2.46%), MRI in 4 cases (3.29%) and CT in 5 cases (4.1%). In 2 cases, CT and MRI were both performed (1.64%). No imaging tests were performed in 8 cases (6.56%), and in 20 cases (16.39%) the authors did not provide information.

Table III. Clinical presentation

Symptom	Number of cases	Rate
Breast size enlargement	102	83.61%
Breast lump	19	15.27%
Axilar lump or lymphadenopathy	13	10.66%
B symptoms	6	4.29 %
No symptoms	5	4.1%
Abscess	1	<1%
Galactorrhea	1	<1%

** Several patients referred more than one symptom when consultation*

Histological diagnosis

To confirm the diagnosis, cytology of the periprosthetic seroma by puncture was performed in 64 cases (52.46%), followed by surgical biopsy of the periprosthetic capsule. In 8 cases, only the cytology of the seroma (6.56%) was performed. A mass or periprosthetic capsule biopsy was performed in isolation in 45 cases (36.86%), and was carried out in 30 cases (24.59%) in the operating room. In 5 cases (4.1%) no information was provided.

The pathological diagnosis of ALCL was obtained prior to its surgical treatment in 69 cases (56.56%). In 50 cases, the diagnosis was during the postoperative period, after analyzing samples obtained during the prosthetic explant and capsulectomy. In 3 cases (2.36%) the authors did not specify this information.

In 120 cases (98.36%) the ALCL diagnosis was confirmed. In 12 cases (9.84%) ALCL affected the periprosthetic seroma only, without capsular invasion. In 2 cases (1.64%), the diagnosis could not be confirmed: in 1 case there were diagnostic doubts between ALCL-BIA and cutaneous ALCL, and in the other case a preoperative cytology with positive result for ALCL could not be confirmed after surgery (Table IV).

Immunohistochemical markers and histology

The markers description was nonuniform. In 20 cases (16.4%) the authors did not specify what type of markers were studied and only described the diagnosis as positive for ALCL-BIA. In 21 cases (17.2%) the only markers identified to make the diagnosis were CD30 +, ALK-. While in 81 cases of 122 (65.6%) a broad and specific description of markers that were studied to reach the definitive diagnosis was provided. These include: CD30, CD2, CD3, CD4, CD8, EBER, TIA1, CD5, CD7, CD10, CD20, CD45, BCL-6, CD138,, CD43, CD45RO, CE79A, PAX, CD56, CD34, CD68, CD163, CD15, CD45, Epi-

Table IV. Histological tests

Diagnostic tests	Number of cases	Rate
Peri implant seroma (cytological test). Capsule biopsy	64	52.46%
Lump/Lymphadenopathy/Capsule biopsy (preop.)	15	12.30%
Lump/Lymphadenopathy/Capsule biopsy (postop.)	30	24.6%
Peri implant seroma (cytological test). (pre. or postop.)	8	6.56%

** In 5 cases sample retrieval was not referred*

thelial membrane protein (EMA), keratin (AE1 / AE3), S100, CD68, HMB45, CD79a, CD138, kappa, lambda, GRANZIMA, PAX5, EBV HHV8, CKAE1 / AE3, CD34, BCL-2 , Ki-67, CK7, CK19, CK20, E-cadherin, Her2, ER.

Regarding the characteristics of the cells in histological studies, they were similar to those of systemic large-cell anaplastic lymphoma, in their nodal or extranodal location.[12] The cells were large, with pleomorphic and anaplastic morphology, and abundant eosinophilic cytoplasm. The nuclei were large, oval or multilobed, with dense chromatin, and usually had prominent nucleoli with frequent mitosis images. Kidney-shaped cells were found in 70% of cases.[13]

Breast implants

Regarding prosthetic material, 27 patients (22.13%) of the 122 cases studied were carriers of different implants throughout their personal history due to multiple replacements. On the other hand, 95 (77.8%) cases only had one type of implant. The prosthetic material was unknown in 16 (13.1%) cases, silicone in 74 (60.7%) cases and saline in 29 (23.8%) cases. In 3 (2.5%) cases, implants used were both silicone and saline. In terms of implant cover texturization, in 55 (45%) cases this parameter is unknown, while in 67 (55%) textured implants were used.

In our review 2 patients had smooth implants, but they belong to the group of patients who had more than one type of implant throughout their personal history. One of them had a textured implant and the other had polyurethane (PU) foam coating prior to disease diagnosis. None of the case reports clarify what kind of texturization method was present. Of the 122 cases reviewed, 9 (7.4%) were coated with polyurethane foam.

Implant brand was better documented, although in 57 (46.7%) brand name and implant type used prior to diagnosis was completely unknown. In cases where patients had only one implant, or more than one, but without changing brand name, the following cases were reported: 6 cases of polyurethane foam coated implants, 4 of which were Silimed™ and the other 2 were not specified. 47 cases had Allergan™ implants in all its variants (Mc Ghan™, Inamed™, Biocell™, Natrelle™), 3 cases were Nagor™, 1 was Eurosilicone™ and 1 was PIP™. In cases with patients carrying more than one brand of implant, which were well documented, the following data was available: 4 cases Allergan™, 3 cases Mentor™, 2 cases Silimed™, 1 case Polytech™, 1 case Nagor™ and 1 case Rofil™ (Table V).

Genetic and mutational review

In our revision, no genetic studies were carried out in any of the 122 notified cases. Nonetheless, Li-Fraumeni syndrome, related to TP53 gene mutations, was present in 2 patients who were diagnosed with BIA-ALCL following breast cancer reconstruction with breast implants.

Treatment

In this sense, 57 (47%) cases were observed where the stage of the disease was not known. On the other hand, in 28 (23%) cases non-surgical treatment was unknown, whereas 12 (10%) cases had no information about surgical treatment. In the cases where details where known, the description was made in a variable and ununiform fashion. Finally, breast reconstruction following treatment was unknown in 102 (84%) cases.

Table V. Case report, manufacturers and texturization system

Manufacturer	Cases	Texturization system
ALLERGAN-INAMED-Mc GHAN	51	Salt elution
SILIMED (PU)	6	Polyurethane foam
NAGOR	4	Unknown
MENTOR	3	Negative-contact, stamp
POLYTECH (PU)	1	Polyurethane foam
Others (PROFIL-PIP-EUROSILICONE)	3	
Unknown	57	

**Total number is more than 122 cases. Every implant identified by manufacturer has been included.*

In order to establish a relation between stage of disease and treatment, a division was made based on available data. Disease stage was described as local disease (regarded as Ann Arbor I) in 43 (35%) cases. Metastatic disease or advanced disease (regarded as Ann Arbor >1) was notified in 22 (18%) cases. It is important to mention that this parameter was unknown in 57 (47%) cases, making interpretation of this data difficult. Surgical treatment will be presented overall, and there will be special mention dedicated to the 22 advanced disease cases regarding medical and surgical treatment.

In the case of surgical treatment, capsulectomy and implant removal was performed in 99 (81%) cases, of which 13 cases had additional treatment, as will be noted further ahead. Surgical treatment was unknown in 12 (10%) cases. Implant removal without capsulectomy was performed in 7 (6%) cases. No surgical treatment was received in 1 case. Lymphadenectomies were performed in 5 (4%) cases (of these: 3 were performed together with mastectomy, 1 with implant removal and 1 with implant removal and capsulectomy). In total, 8 (7%) tumorectomies were performed (of these: 2 with no further treatment, 5 with implant removal and capsulectomy, 3 with implant removal alone). In 2 cases, affected lymph nodes were excised, together with implant removal and capsulectomy. A total of 5 (4%) mastectomies were performed (of these: 3 cases together with lymphadenectomy, as previously mentioned). Furthermore, 2 cases of partial mastectomies were described, both with implant removal and capsulectomy. In one case, surrounding erythematous skin was removed, finishing treatment with implant removal and capsulectomy. In the group of 22 cases of documented advanced disease, the following results were obtained in terms of surgical treatment: implant removal and capsulectomy were performed in 16 cases (of these: 2 with tumorectomy, 2 with mastectomy and lymphadenectomy, 2 with lymph node excision). Implant removal without capsulectomy was performed in 5 cases (of these: 4 with no further treatment, 1 with tumorectomy). In 1 case no surgical treatment was received.

Non-surgical treatment in the reviewed cases was variable. In 40 (33%) cases no treatment was received by patients, whereas this parameter was unknown in 28 (23%) cases. The most common treatment was chemotherapy (CT) combination of cyclophosphamide, vincristine, doxorubicin and prednisone (CHOP), which was administrated on its own in 21 (17%) cases. CHOP was used together with radiotherapy (RT) in 13 (11%) cases and with brentuximab in another 2 cases. On the other hand, RT was administrated on its own in 6 (5%) cases. Besides the cases combined with CHOP, brentuximab vedotin was administrated in 2 cases on its own, and in another case brentuximab was combined with RT. In 6 cases, treatment was only described as ¨chemotherapy¨ (of these: 2 were combined with RT). In 3 cases, hematopoietic stem cells were used. Other medications administrated seldomly include etoposide, bortezomib, metotrexate and combinations: CHOEP, CEOP, HSCT, V-EPOCH, R-CHOP. In the following section, we will describe treatment in advanced stage disease.

In terms of non-surgical treatment, the following information was collected in the 22 cases of advanced disease. CHOP was administered in 5 cases on its own. CHOP was combined with RT in 1 case and etoposide in another case. In 1 case, CHOP was administered, followed by cytarabine, methylprednisolone, etoposide and cisplatin, without results. This patient achieved complete remission with brentuximab vedotin and hematopoietic stem cell transplant was programed. In 1 case, brentuximab vedotin was administered on its own. 1 case was described in which treatment consisted in cyclophosphamide, doxorubicin and prednisone (CHP) with RT. In 2 cases, CHP was combined with brentuximab vedotin. CHOEP and CEOP was used in 1 case. In 1 case, R-CHOP was combined with RT, and in another case, CHOP was combined with metotrexate and autologous transplant of bone marrow. 2 cases were described in which neoadjuvant treatment was used (of these: 1 with CHOP and the second with cisplatin and gemcitabine, with no result in the latter case). In 1 case, CHOEP and HSCT was administered. In 1 case, cyclophosphamide, doxorubicin, etoposide, prednisone and RT were combined. In 1 case, RT and brentuximab were administered. In 1 case V-EPOCH, bortezomib, intracranial prophylactic CT, metotrexate and RT were administered. In 1 case the combination used was cyclophosphamide, hidroxi-daunorubicin, vincristine and prednisone.

Regarding breast reconstruction after treatment, few details are known. This parameter was absent from communications in 102 (84%) cases. Reconstruction was not conducted in 6 (5%) cases. Documented reconstructed patients were a total of 14 (11%). Within those 14 patients, information is again scarce. In 5 cases immediate breast reconstruction was conducted, in 8 cases reconstruction was done in the first year and in 1 case reconstruction was conducted 2 years after initial surgical treatment. In the 5 cases of immediate breast reconstruction, in 2 cases the procedure was carried out with smooth implants and in 3 cases no information was available. Within the 8 cases of reconstruction inside the first year post-treatment, 2 were free flap autologous tissue (Deep Inferior Epigastric Perforator Free Flap) and 1 case was conducted with autologous fat transfer. As for the other 5 cas-

es, 2 were by means of implant (1 smooth, 1 unknown) and 3 cases did not describe the technique that was used. Lastly, in 1 case breast reconstruction was carried out two years post-surgical treatment, by means of implant, without details about the type of implant used.

In our review, 95 (77.8%) of the 122 were in remission in the moment of publication of the case reports. 5 patients presented relapse and there were 5 deaths (4%). In both cases, this was associated to advanced stage of disease on time of diagnosis.

Discussion

Interest regarding LACG-AIM has increased in recent years. Investigations referred to the cause of this event are also growing. Several theories have been put forward but pathogenesis of this type of lymphoma is far to be completely understood. Immune system chronic stimulation originated either by the implant or by the presence of high amounts of gram-negative bacteria are the two most relevant theories that have been proposed.[14,15] Allergic mechanisms (IL-3 activation) and genetic susceptibility have also been described.

Nowadays, implant texture type has been recognized as a relevant factor in the pathogenesis of this disease. This fact can influence not only the choice of the type of implant to be used but also the whole breast reconstructive procedure. It can even affect the will of the patient to undergo an aesthetic augmentation. In spite of the fact that manufacturers have the legal obligation of characterizing the type of texturization according to ISO 14607:2018-Annex H,[17] provided description is more related to marketing issues than safety, generating confusion.[18] In addition, polyurethane implants may cause misunderstanding, when commonly mistaken as being macrotextured.[19]

In December 2018, CE-marking for Biocell™ and Microcell™ (Allergan) was removed,[20] leading to marketing restriction in Europe and related countries. In April 2019, French Agency, ANSM (Agence Nationale de Sécurité du Médicament et des Produits de Santé), banned every macrotextured and polyurethane implant involving different manufacturers such as Sebbin™, Polytech™, Nagor™, Eurosilicone™, Arion™ and Allergan™.[21]

In July 2019, FDA issued a news release where a new total of 573 unique cases globally of BIA-ALCL and 33 patient deaths were referred. Specifically, of the 573 unique cases of BIA-ALCL, 481 are attributed to Allergan™ implants. Of the 33 patient deaths the FDA is reporting today, 12 of the 13 patients for which the manufacturer of the implant is known, are confirmed to have had an Allergan™ breast implant at the time of their BIA-ALCL diagnosis.[22] FDA then issued Biocell™ implants to be removed from the trade market and Allergan™ reaction was total removal. In the iberolatinoamerican market, Biocell™ implants have completely disappeared, but in Spain and Portugal only Microcell™ CE-marking has been considered. Other manufacturers have not been involved.

Limitations of this review include major differences in the information provided in the literature referred to absence of data regarding type of implant, texturization, manufacturer, presence of subclinical infection/biofilm or postop reconstruction. This fact encourages us to manage data with extreme caution.

Regarding symptoms, typical form of presentation of LACG-AIM includes a late seroma in a patient bearing breast implants. Medium time since implantations is nine years.[7] According to Quesada, a seroma should be considered as "late" when more than one year since implantation has passed. If this occurs before the first year, hematoma, infection or immediate surgical complication should be supposed. Other forms of presentation include palpable breast lump (8-24%), axillary lymphadenopathies (4-12%) or cutaneous involvement (5%).[7]

In our review, the most common form of presentation was breast size augmentation caused by late seroma. In addition, frequency of palpable lumps and lymphadenopathies were consistent with those previously published by Clemens[7] (15.57% and 10.66%, respectively). Cutaneous involvement as exclusively first symptom was rare (<1%).

Referred to diagnosis, if suspected, ultrasonography should be performed to detect peri implant fluid, breast lumps or axillary, internal mammary or supraclavicular enlarged lymph nodes.[7] When ultrasonography is negative but clinical suspect persists, MRI is recommended. In this review MRI was performed in 80 cases (65.57%) alone or in combination with other diagnostic imagery procedures (predominantly mammography or CT scan). Extension studies with CT or PET-CT scan have not been evaluated, as they were not considered to be the aim of this review. Since 2016 there is a shift in the paradigm of diagnostic imagery procedures protocol. Before that year, ultrasonography was performed in 45% of the cases (30/55). Later, this rate increased to 68.66% (46/67).

Pathological diagnosis should be performed through cytological exam of seroma and peri implant scar capsule biopsy. When LACG-AIM is suspected and seroma is detected, this fluid should be sent to cytological testing, flow cytometry and immunohistochemical exams with specific markers. If lumps are present, a biopsy is mandatory.

In the present review, fluid cytological exam (retrieved by puncture) was performed in 64 cases (52.46%) followed by peri implant scar capsule biopsy confirmation. No difference referred to the rate of performance of these two techniques were found before (52.73%, 29/55) or after (52.23%, 35/67) 2016. It is noticeable that in 45 cases no previous seroma fluid study was performed achieving diagnosis of LACG-AIM through biopsy of scar capsule, lump or lymphadenopathy.

Diagnostic procedures led to diagnosis of LACG-AIM previous to surgical treatment in 69 cases. This diagnostic rate improved after 2016, changing from 49,09% to 62,69% (27/55 cases before 2016 versus 42/67 after 2016).

Regarding results achieved in our review, a better diagnostic approach has been appreciated as knowledge of this disease increased, and guidance documents became available as those published in Consensus Guidelines on the Diagnosis and Treatment of Breast Implant-Associated Anaplastic Large Cell Lymphoma (NCCN).[7]

When considering data related to the type of implant, as previously referred, it is remarkable that 100% of lymphoma cases, when this information was available, occurred in texturized breast implants bearers. No data related to smooth implants was available.[7] In albeit, FDA notified in March 2018 30 cases of LACG-AIM in patients with smooth implants. Data from clinical registers were insufficient and no relationship could be firmly established.[23]

No publication referred type of texturization (which is extremely relevant considering the strong association with macrotexturization or with specific texturization methods). In any case, in this review, a stronger association was found for Allergan™ implants.

With respect to surgical treatment, more data were provided. Only in 12 cases (10%) surgical procedure was not referred. The most frequent procedure was implant removal together with capsulectomy (99 cases, 81%). Implant removal with no reference to capsulectomy was performed in 7 cases (6%).

As previously mentioned, 2016 changed the knowledge and approach to this disease. Considering this, surgical attitude before this date is deeply analyzed. Jarjis et al. published before 2016 implant removal with no capsulectomy. Recurrence 4 years later happened and capsulectomy was finally performed. Zimmerman also published his experience before 2016. No implant removal or capsulectomy were performed at the moment of diagnosis. Recurrence also took place and both implant removal and capsulectomy were then performed. Gaudet reported a case in 2002 of a 59-year-old female with advanced disease treated with chemotherapy. No reference to surgical treatment was done. Recurrence happened one year later. Other references before 2016 with no implant removal or capsulectomy were those published by Ravi-Kumar and Wu (in the second reference this was owed to patient control loss). In addition, and after 2016, Letorneau, Chacko and Alcalá did not perform implant removal or capsulectomy. Recurrence happened both in Letorneau and Chacko reports.

In conclusion, the most accepted treatment for LACG-AIM is implant removal and capsulectomy. This attitude is supported by evidence of recurrence when those procedures were not performed.

Related to genetic anomalies associated to LACG-AIM, no relevant information was provided in analyzed literature. Only JAK1/STAT3 mutations with activation of this pathway were described.[24] Additional mutations were referred in SOCS1 (Suppressor of Cytokine Signaling 1), JAK/STAT pathway regulator. Oncogene activation JunB and SATB1 and TP53 abnormalities have also been described. The absence of information is probably due to the lack of knowledge referred to these issues. More data and publications should be expected in the future.

Furthermore, the relatively low rate of publication in the iberolatinoamerican community is surprising[8,25-28] considering that following information referred by ISAPS,[29] the most important volume of aesthetic procedures in the area of breast augmentations comes from our community. This fact should encourage all of us to gain presence in the literature by publishing every experience regarding this specific issue, or all our plastic surgery practice in general.

Finally, the control by Health Authorities referred to breast implants should be considered of key relevance, not only for detection purposes but also for evolution control. National registries should be mandatory. They support better knowledge about diagnosis, treatment, risk/benefit ratio of implants leading to a more accurate knowledge of etiology for LACG-AIM. UK, France, Germany, Netherlands, US or Australia have developed breast implant registries. Since 2018, the Spanish Breast Implant Registry (SREIM) allows Spanish surgeons to notify to the AEMPS (*Agencia Española del Medicamento y Productos Sanitarios*) any issue related to breast implants. The active use of this tool is basic for patient safety.[30]

In 2006, FDA recommended implant manufacturers to create an ID card that should be given to patients after surgery, including detailed data of implants. In the present time Health Agencies are requesting manufacturers transparency, and inclusion of additional data in the ID card as unique ID device number, warnings and label-

ling. This would allow patients to gain access to updated information through the webpage of manufacturers.

In summary, a lack of consensus among Health Regulatory Agencies is patent with opposite positions adopted with no clear justification. In addition, a more active attitude by professionals, authorities and, of course, manufacturers should be advisable. It is certainly surprising that recurrently, implants or medicines issues occur. Fast and energic regulatory measures should be promptly taken.

Conclusions

Since the first report of a case series in women with T cell lymphoma associated to breast implants 24 years ago, a long, but not exemplary, clinical, therapeutic and regulatory has been made.

Literature research has shown that references mainly consist of case reports and reviews previous to this one, with different approaches and conclusions. Beyond diagnostic, pathogenic or therapeutic issues, retrieved literature is far from being clear or precise when detecting etiological circumstances. This is well illustrated by the fact that in 46.7% of these publications, the manufacturer is not identified. Furthermore, when cited, no information regarding texturization or the manufacturing procedure is provided. This unclear database is possibly the main reason for the lack of knowledge related to this disease.

In addition, Health Regulatory Agencies in different countries act in different ways, adopting sometimes opposed legal measures.

We are concerned about the need of a deeper and more conscious involvement of every actor in this scenario in order to achieve higher transparency and credibility.

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