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Breast

Breast Implant–associated Anaplastic Large Cell Lymphoma in Colombia: Report of a Multidisciplinary National Registry

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Background: An estimated 43,390 breast augmentation surgeries (86,780 implants) and 1486 breast implant reconstructions are performed annually in Colombia, representing the second-most breast surgery destination in South America, the fourth in the western hemisphere, and the fifth country worldwide. No previous reports have evaluated the incidence of breast implant–associated anaplastic large cell lymphoma (BIA-ALCL) epidemiology or outcomes in a Hispanic population. Published data on the incidence of this disease in Colombia are unknown; therefore, a National Joint Multidisciplinary Committee was developed between the Colombian scientific societies of Mastology, Plastic Surgery, Hemato-Oncology, and the Invima (The National Food and Drug Surveillance Institute) to track national cases of BIA-ALCL.

Materials and Methods: We performed a retrospective review (survey-based study) of historical cases since 2011–2019, and a prospective collection of all patients with a confirmed World Health Organization diagnosis of BIA-ALCL identified in a newly established National Registry of BIA-ALCL. The trial was approved by Institutional Review Board (IRB).

Results: Eighteen cases of BIA-ALCL were identified in Colombia between 2011 and 2019. Hundred percent developed as sequelae of textured implants. Six patients (33.3%) presented either a peri-implant capsule mass or axillary lymph node involvement. Seven (38.9%) required adjuvant chemotherapy most commonly with CHOP regimen. Different brands of implants were associated with our cases. One death (5.6%) was attributed to BIA-ALCL, and one (5.6%) case displayed with relapsed with bone marrow involvement requiring a bone marrow transplantation. Six cases (33.3%) were identified with advanced stage (IIB-IV). Disease-free survival of 92.3% was achieved at 30.8-month follow-up.

Conclusions: Colombia has one of the highest volumes of breast surgery and use of textured surface breast implants in the world. This study is the initial report of an implant registry in South America. A high proportion of advanced disease may be a consequence of delayed presentation, lack of disease awareness, and timely access to tertiary cancer centers for diagnosis and treatment. Brands other than Allergan and Mentor were found to be associated with BIA-ALCL in our study. *(Plast Reconstr Surg Glob Open 2020;8:e3013; doi: 10.1097/GOX.0000000000003013; Published online 18 August 2020.)*

INTRODUCTION

In 1997, Keech and Creech[1] made the first report of a 41-year-old patient with textured surface breast implants who developed a 2-cm mass adjacent to the implant capsule, with the diagnosis of anaplastic lymphoma. The appearance of the tumor was described as seeming to be a consequence related to the inflammatory reaction

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surrounding the implant. Breast implant–associated anaplastic large cell lymphoma (BIA-ALCL) is now recognized as a rare and emerging type of lymphoma by the World Health Organization[2,3] (Fig. 1). Importantly, BIA-ALCL appears to be indolent in contrast to systemic ALCL, which are usually highly aggressive malignancies with poor prognosis.

In 2011, the US Food and Drug Administration (FDA)[4] released a safety communication warning about the risk of this disease, generating a report from approximately 34 world cases. In 2011, Carty et al[5] reported the first case of a deceased patient with this diagnosis. The FDA has subsequently released annual reports. The most recent paper, published July 24, 2019, updated to 573 BIA-ALCL pathologically confirmed cases and 33 deaths related to the disease.[6] At this time, the FDA called for a class I recall of Allergan Biocell textured tissue expanders and implants, which subsequently expanded to a worldwide recall. Multiple publications in the United States,[7–10] Europe,[11] and Australia[12] have previously reported about the epidemiology and risk of the disease. Calculated Implant-Specific Risk of BIA-ALCL per Number of Implants according to the Australian group. Silimed polyurethane 2832 (1582–5673) Biocell 3345 (2475–4642) Siltex 86,029 (15,440–1,301,759).[12] BIA-ALCL occurs following both aesthetic surgery and breast cancer reconstruction. Because of rarity of disease, it is critical to establish a centralized disease database to allow identification and follow-up of patients with breast implants, such as the Patient Registry and Outcomes For Breast Implants and Anaplastic Large Cell Lymphoma (ALCL) Etiology and Epidemiology (PROFILE) (www.thepsf.org/PROFILE) BIA-ALCL registry of the American Society of Plastic Surgeons in the United States.[13] As of August 2019, PROFILE has identified 288 US cases as part of 711 cases over 35 countries.

The exact cause of BIA-ALCL remains unknown. Multiple factors have been implicated[14] (14), including the use of textured surface implants, a local inflammatory reaction,[15] and impaired host immunity by mutations in the *JAK3-STAT* pathway and *MYC/TP53* deregulation.[16–18] The average time from implant to lymphoma development is approximately 9 years.[19] The most frequent clinical manifestation is the presence of limited effusion (seroma), which occurs in almost 70% of cases. The presentation with an infiltrative pattern in the form of mass is less frequent and is usually more aggressive with a worse prognosis.[19]

An estimated 43,390 breast augmentation surgeries (86,780 implants) and 1486 breast implant reconstructions are performed annually in Colombia, compared with approximately 217,000 in Brazil and 331,000 in the United States.[20] Although sporadic cases with BIA-ALCL have been reported from Colombia,[21] there are no reports evaluating the incidence of BIA-ALCL epidemiology or outcomes in Colombia or any other Latin American country. Therefore, a National Joint Multidisciplinary Committee was formed between the Colombian scientific societies of Mastology, Plastic Surgery, the Colombian Society of Hematology

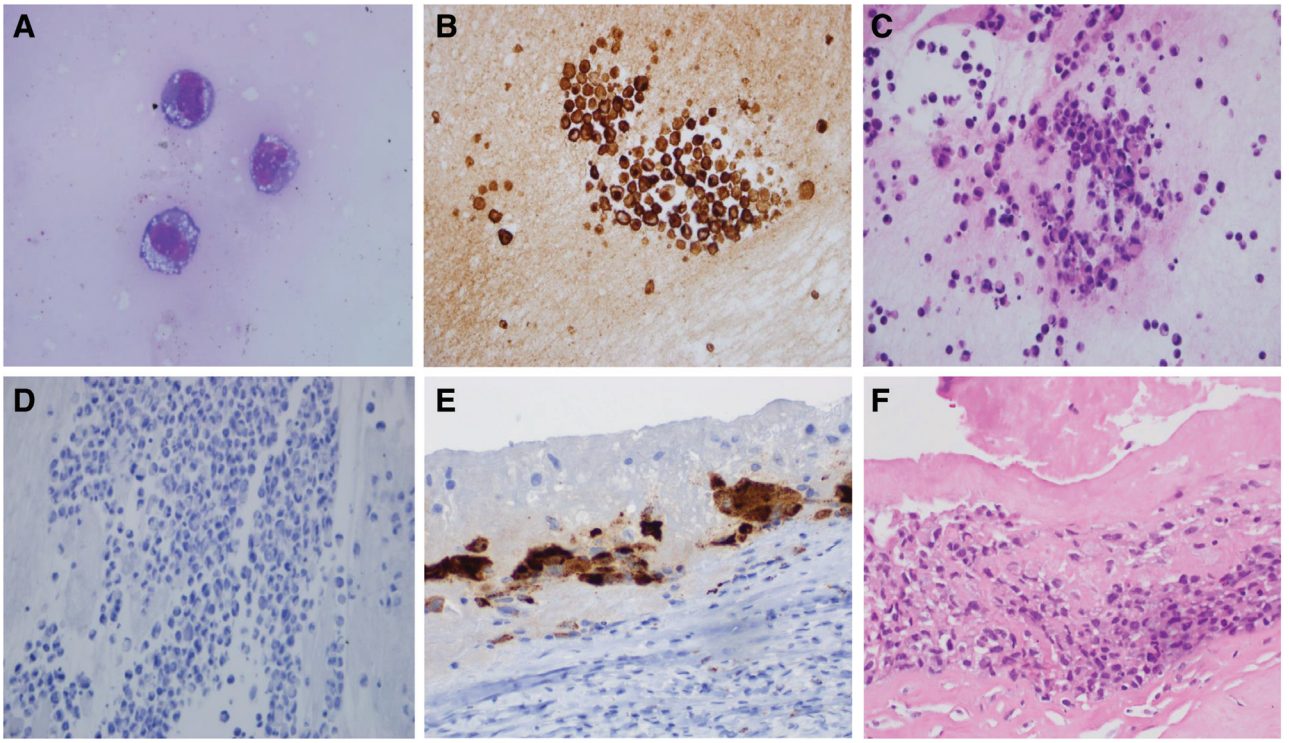

Fig. 1. Pathologic appearance demonstrating large anaplastic cells and confluent staining with CD30 immunohistochemistry characteristic BIA-ALCL. A, Block lymphocytes cellular. B, CD 30 positive. C, Abundant T lymphocytes in cell block (cito spin). D, Alk negative. E, Positive granzyme. F, T lymphocytes adhered to the patient capsule with diagnosis of BIA-ALCL. Images courtesy of the Department of Pathology, Clinica Las Americas.

and Oncology (Asociacion Colombiana de Hemato Oncologia; ACHO), and The National Food and Drug Surveillance Institute (Invima) to track national cases within this population and to develop a consensus to standardize education on disease awareness and improve the identification and diagnosis of patients with BIA-ALCL (Fig. 2). The purpose of this survey-based study is to develop a Colombian registry to evaluate the frequency of this disease and the clinical behavior of the BIA-ALCL in Colombia.

MATERIALS AND METHODS

We performed a retrospective review of historical cases between 2011 and 2019 and a prospective registry of all patients from January 2018 to December 2019 with a confirmed diagnosis of BIA-ALCL following established in the literature.[2,22] Unique cases were identified in a newly established National Registry of BIA-ALCL, that encompasses Colombian societies of plastic surgery (Sociedad Colombiana de Cirugia Plastica y reconstructiva), breast cancer surgery (Asociacion Colombiana de Mastologia), hematology and oncology (Asociacion Colombiana de Hemato-Oncologia), and pathology (Asociacion Colombiana de Patologia). Patients who had confirmed histologic diagnosis of ALCL and were negative for anaplastic lymphoma kinase (ALK) by immunohistochemistry or fluorescence in situ hybridization arising around breast implants were selected. The study was presented and approved by an Independent Research Ethics Committee (Institutional Review Board). Through an electronic survey, information was requested from 3000 national doctors of the 4 specialties (plastic surgery, hemato-oncology, breast surgery, and pathology) for the occurrence of suspicious or confirmed cases. The search for cases included the following parameters: women of ≥18 years old, history of breast implantation, and confirmed histologic diagnosis of ALCL. Once a case was identified, the treating physicians contacted patients to obtain informed consent for participation in the study. Exclusion criteria were patients not consenting to participate in this study, patients with ALCL but without a history of implants, or patients with a histologic diagnosis of ALCL confirmed elsewhere without ALCL involving a breast capsule. Clinical data were collected from review of charts and/or electronic medical records by referring clinicians or the authors with authorization and included demographics, clinical characteristics such as age at the time of diagnosis, the reason for implants (reconstruction or cosmetic), the surface of the implant (smooth or textured), clinical presentation as effusion or mass, history of previous surgery or other medical intervention related with the implant, therapy received (surgery, chemotherapy, radiation therapy), follow-up, and outcomes. Imaging studies were reviewed by radiologists who are experts in breast imaging. Expert hematopathologists retrospectively examined the pathologic reports and diagnostic material. Gross and microscopic pathologic characteristics were retrieved from pathologic reports and from reviewing all cytologic and histopathologic specimens. A pathologic stage was determined as recommended.[2,3,22,23] The tumor cell phenotype was determined by immunohistochemistry or flow cytometry immunophenotype. Survival analysis was measured from the diagnosis to the date of the patient's last live

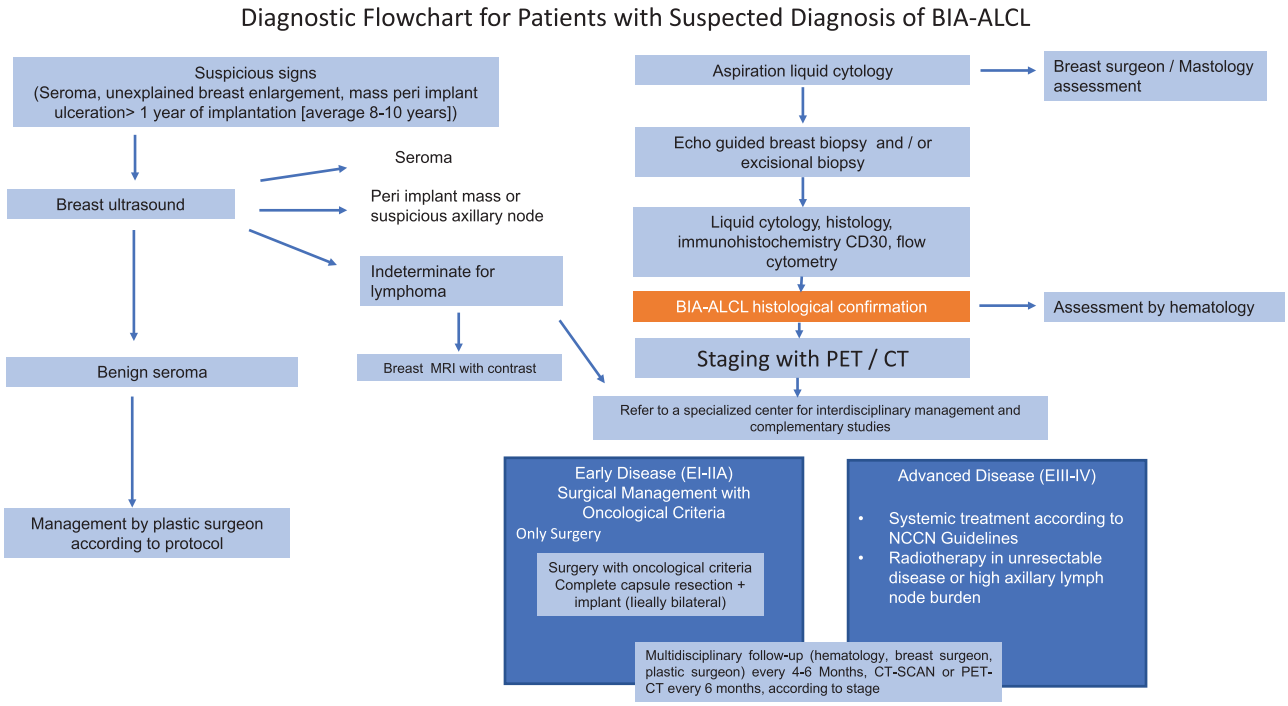

Fig. 2. Diagnosis and treatment flowchart by the Joint Multidisciplinary Societies in Colombia for BIA-ALCL management. (Adapted from National Comprehensive Cancer Network Guidelines, www.nccn.org). CT, computed tomography scan; EI-IIA, stage I-IIA; EIII-IV, stage III-IV; NCCN, National Comprehensive Cancer Network; PET, positron emission\tomography.

control. For deceased patients, written authorization was requested from one of their relatives. Information analysis was performed using Stata V14 (StataCorp. 2015, Stata Statistical Software: Version 14; StataCorp LP, College Station, Tex.). Univariate analysis was performed. Overall survival (OS) and disease-free survival (DFS) were considered primary outcomes. OS was calculated from diagnosis date to last live control, and DFS was calculated from diagnosis to relapse or the date of the last patient control.

RESULTS

We identified 18 patients with BIA-ALCL in Colombia between 2011 and 2019. The median age at diagnosis was 50 years (range, 35–68 years). The reason for implants was esthetic augmentation in all patients. The filling of implants was silicone in 17 of 18 (94%) cases and saline in 1 (6%). The surface of implants was macrotextured, as determined by the International Standard Organization classification in all 18 patients. The manufacturers were reported as Allergan in 7 (38.8%) patients, Mentor in 3 (16.6%), Silimed Polyurethane in 2 (11.1%), and one of each for patients who received Eurosilicone, Nagor, Orion, and Poly Implant Prothèse (PIP). The manufacturer was not determined in 2 (11.1%) patients. The average time from the first implant implantation to diagnosis was 10.5 years (range, 2–33 years). A history of previous surgical interventions for implants revealed that 10 of 18 (55.5%) patients had a unique set of implants, while 7 (38.9%) had 1 previous replacement, and 1 (5.5%) patient had >4 implant changes.

The clinical presentation was delayed seroma in 11 of 18 (61.1%) patients, peri-implant mass in 3 (16.7%), axillary lymphadenopathy in 3 (16.7%), and breast pain with tenderness in 1 (5.5%) patient.

All patients (100%) received complete capsulectomy as a first intervention after diagnosis. In addition, 15 (83.3%) patients had bilateral implant removal (Fig. 3), and 3 (16.7%) had unilateral implant removal. In addition, only 1 patient received immediate reconstruction with smooth surface implants.

The diagnosis was confirmed in 77.8% (N = 14) of the cases using peri-implant fluid flow cytometry. On 3 occasions, an excisional biopsy was required to establish the diagnosis (16.7%; N = 3), and one axillary lymph node core needle biopsy (5.5%) was performed.

Extent of disease was established using positron emission tomography-computed tomography (PET-CT) in 77.8% of patients (N = 14), magnetic resonance imaging in 11.1% (N = 2), and breast ultrasound in 11.1% (N = 2). The clinical stage, according to Clemens et al,[24,25] was stage monoclonal antibodies (AI/AB) in 11 (61.1%) patients, stages II and III in 6 (33.3%), and stage IV in 1 (5.6%) patient with bone marrow involvement (Fig. 4).

Pathologic Features

Immunohistochemical analysis showed positive for CD30 and negative for ALK in 100% of the pathologic studies.

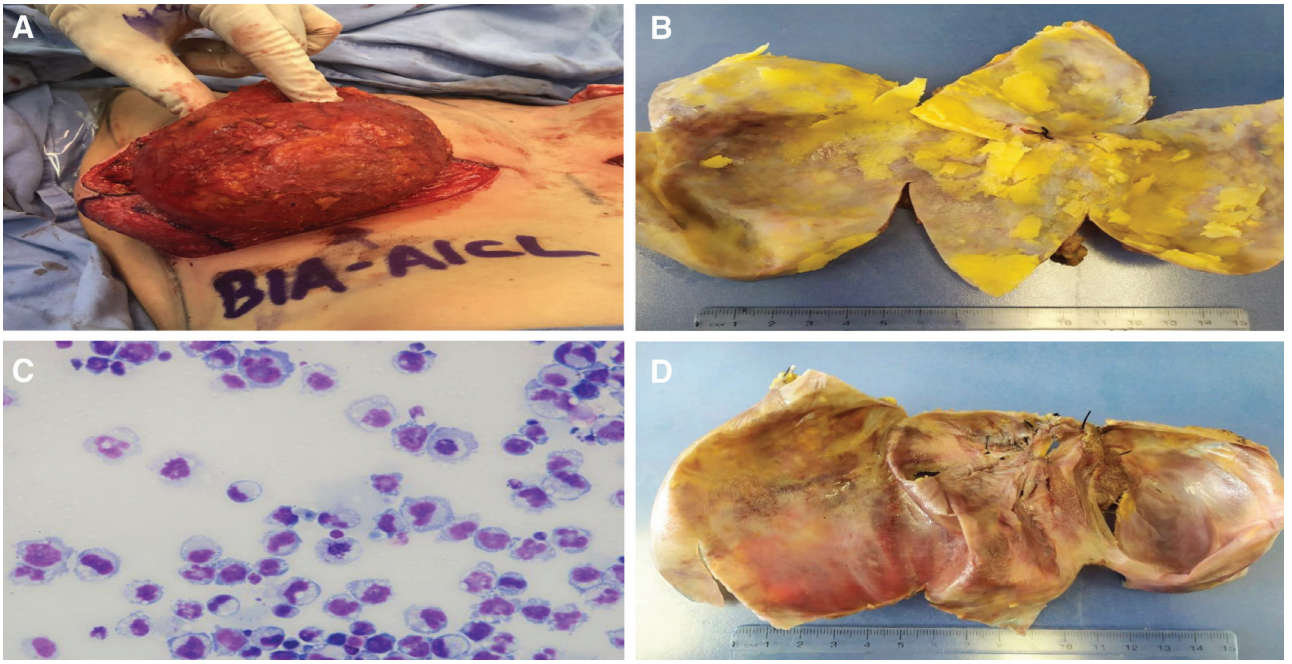

Fig. 3. A, En-bloc resection of the capsule with the implant according to the protocol of the Md Anderson cancer center. B, Atypical lymphoid infiltrate present on the surface of the fibrous capsule. C, Marked atypia, anaplastic cells of large size correlation with flow cytometry 40 X Diff-Quick. D, Smooth surface of the implant capsule without suspicious lesions. Compare with (B). Images courtesy of the Department of Breast Pathology, Clinica las Americas Medellin Colombia.

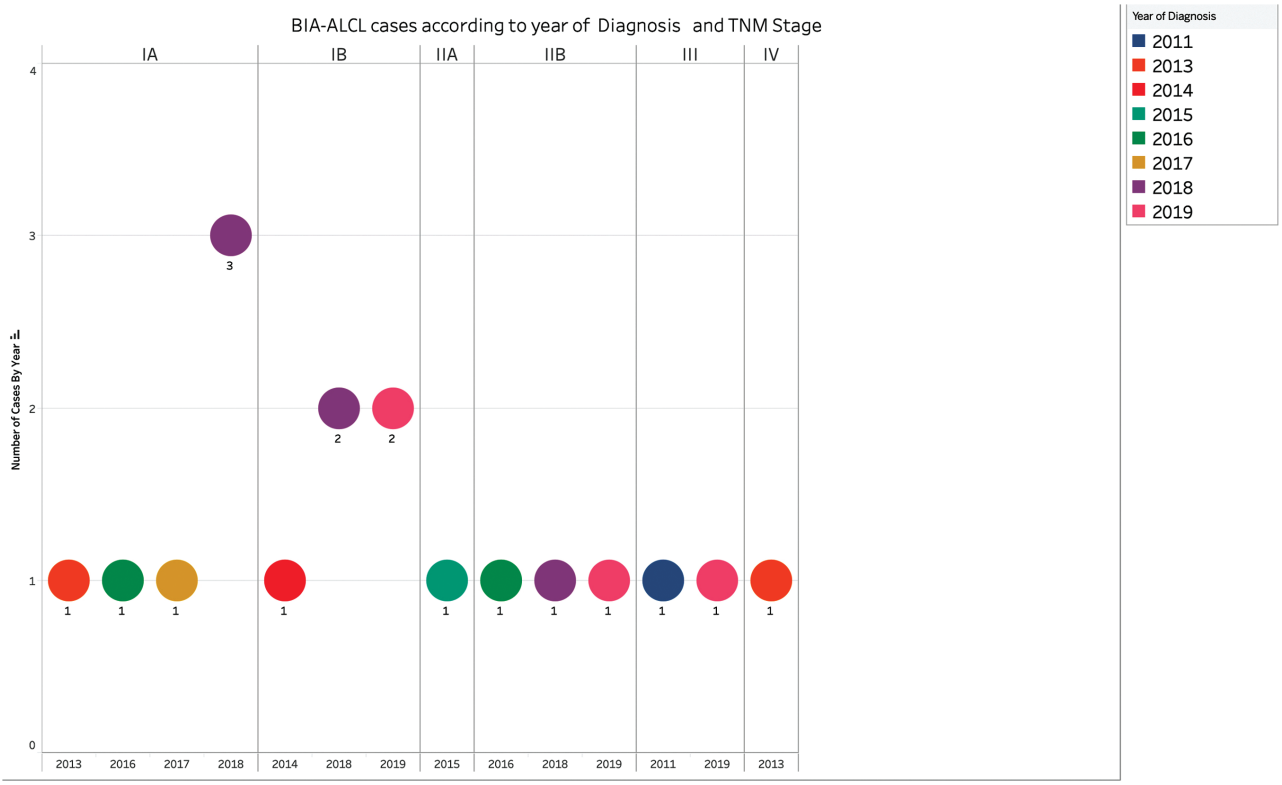

Fig. 4. Year of diagnosis of BIA-ALCl and stage of the cases identified (notice increase in early stages in the last 2 years). TNM, Tumor, Nodes, Metastasis Classification of Malignant Tumors.

Therapy and Clinical Follow-up

Seven patients received chemotherapy, which consisted of cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP) for 3 patients and CHOP plus etoposide (CHOP + E) for 4 patients. None of our patients received brentuximab vedotin–targeted immune therapy because in Colombia, its use has not been approved in BIA-ALCL.

All patients who presented axillary lymph node involvement (n = 6) received chemotherapy; only 1 patient with stage IIA who was in an early stage of the disease received chemotherapy (Fig. 5). DFS of 92.3% was achieved at 30.8-month follow-up.

We identified that the first patient diagnosed with BIA-ALCL in Colombia occurred in Medellin in 2011 and had a clinical stage IIB. The patient received surgical management with bilateral capsulectomy and explantation. However, she did not receive chemotherapy at that time. She had a disease relapse 2 years later confirmed by axillary biopsy and metastasis to the bone marrow. The patient received CHOP + E chemotherapy (6 cycles), followed by chest wall radiotherapy 50Gy given at 2Gy per fraction in 25 sessions over 5 weeks, and subsequently hematopoietic stem cell transplantation (allogeneic). The patient was disease free 6 years after transplant at the last surveillance follow-up.

One patient died due to disease progression. The patient was 52 years old, who presented with axillary lymphadenopathy 9 years after implantation. She had no previous symptoms, neither any type of implant exchange. The clinical staging with total body PET-CT scan showed axillary lymph nodes, and internal and mediastinal mammary nodes were positive. Axillary lymph node biopsy was used to classify and consider the case as clinical stage IV. After diagnostic confirmation, the patient received systemic treatment CHOP, and total capsulectomy with bilateral implant removal after completing 3 cycles of chemotherapy. Shortly after the patient disease progress presented with headache and blurred vision indicates the symptoms and imaging finding central nervous system involvement and expired 9 months after diagnosis. This was the first patient to die of BIA-ALCL in Colombia.

DISCUSSION

BIA-ALCL is an uncommon lymphoma that arises around textured surface breast implants. With almost 900 cases over 33 countries in the world, the clinical spectrum has confirmed initial observations that most patients present effusion around the implants. In contrast, a subset of patients with mass, and occasionally with lymphadenopathy, may develop progressive disease.[2,22,26] It has also been confirmed that when the disease is confined to the capsule around implants, removal of implants and complete capsulectomy or en bloc resection usually leads to cure of the disease.[25] However, the progressive or refractory disease may lead to death in approximately 5% of affected patients.[2,19,25] Therefore, it is essential to develop global strategies to detect and treat in a timely fashion. In Latin America, there are

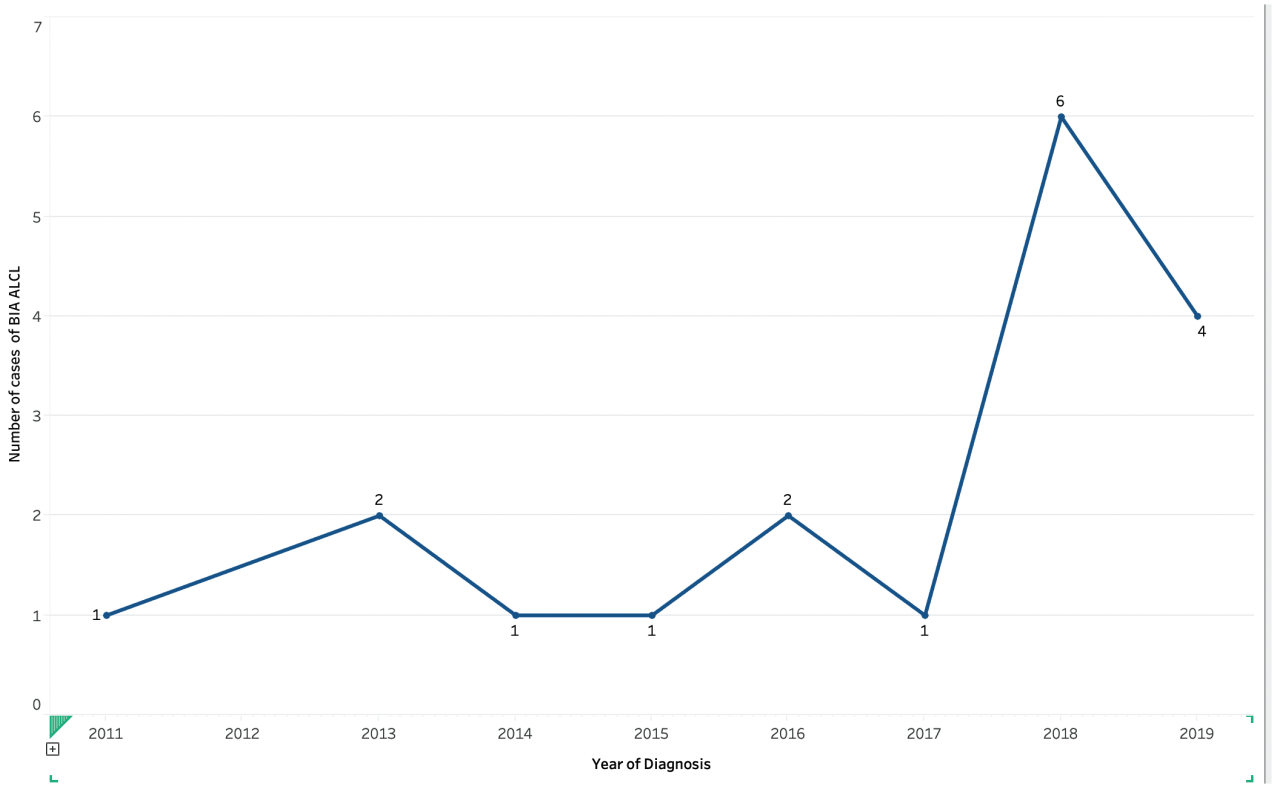

Fig. 5. Timeline by year of diagnosis of BIA-ALCL in Colombia.

no recommendations or policies for surveillance or optimal follow-up of patients with breast implants.[8] Here we detail the results of patient reporting, diagnosis, and follow-up of patients diagnosed with BIA-ALCL in Colombia through the development of a national registry and the multidisciplinary participation of medical society physicians who may encounter patients with BIA-ALCL in their practices.

According to the data published by the International Society of Aesthetic Plastic Surgery,[20] an estimated of 43,390 breast augmentation surgeries (86,780 implants) and 1486 breast implant reconstructions are performed annually in Colombia. The Colombian Association of Plastic Surgery estimates that there are approximately 3 million women with textured surface breast implants implanted in Colombia in the last 20 years.

It is estimated that the incidence of BIA-ALCL in patients with implants is between 1:3000 and 1:30000. If we assume an average of 1 case of BIA-ALCL per 10,000 women with implants, it is expected that approximately 100 cases of BIA-ALCL exist in Colombia. Our multidisciplinary attempt to accrue for patients with BIA-ALCL in Colombia rendered 18 patients, suggesting a marked underdiagnosis of this lymphoma in our country.

This first report of a national effort identified 18 patients with BIA-ALCL, of which approximately 60% presented as delayed seromas, a finding similar to that reported in other series.[2,19] However, in countries such as Australia, where reporting of outcomes has been systematized, there is an increased rate of detection of patients with effusion only.[12] We found that the time from implantation to diagnosis was approximately 10 years, similar to that in other series.[19] However, it is of clinical significance that 8 of 18 patients were diagnosed after 2 medical procedures or interventions, and 1 had multiple procedures before reaching the diagnosis and the patient could receive the appropriate therapy, suggesting a delay in the diagnosis and there is no published literature on the effect of delayed diagnosis in progression of disease. We observed that 33.3% of the cases present node involvement confirmed by biopsy. Ferrufino-Schmidt et al[26] demonstrated that biopsy-proven lymph node involvement occurred in 17% of patients with BIA-ALCL and that lymphadenopathy conveys a decreased OS and lower progression-free survival (PFS).

We found that 6 of 18 (33.3%) patients presented with a peri-implant mass that was grossly visible, which associates with lower OS and lower PFS.[19] All patients with mass received chemotherapy. The diagnosis in advanced stage may be related to the low disease awareness by our specialists because most diagnoses were incidental findings during surgery or subsequently found in pathology review. Of note, cases diagnosed after 2017 have disease in the early-stage compared with our initial cases, which presented with more advanced disease (Fig. 5). Important steps have been taken among our different multidisciplinary scientific societies to educate physicians to become aware of this lymphoma, and hopefully identified the disease in their early stages. These efforts have led to the creation of a national BIA-ALCL Registry and the preparation of a joint document aiming at education and awareness of this lymphoma for doctors and patients.

A number of uncertainties remain regarding BIA-ALCL and its clinical and epidemiologic behavior. The release of sales data is critically important to calculate manufacturer-specific risks. Recently, Cordeiro et al[27] from Memorial Sloan Kettering Cancer Center presented their 20-year single-surgeon prospective cohort study of breast reconstruction in 3546 patients (6023 implants) and identified 10 BIA-ALCL patients. The overall risk of BIA-ALCL in this cohort was calculated by 0.294 cases per 1000 person-years or 1:443 women. A number of questions remain for further studies, such as what are the costs to a health system to identify and treat BIA-ALCL and what are the financial burdens incurred by BIA-ALCL patients. Can partial or total capsulectomies be considered "risk-reducing" in a patient who is disease free and is there a role for prophylactic procedures or screening of asymptomatic patients? What effect does BIA-ALCL risk have on patient and physician preference for micro- and macrotextured implants, and are these preferences shifting? These and other questions should be resolved in the coming years through joint multidisciplinary efforts by our national societies working in collaboration with government authorities to prospectively analyze breast implant long-term outcomes.

The present study has some limitations. The foremost is that this is a retrospective study where the diagnosis was usually made by a referral physician with variable degrees of expertise. There is a perception that physicians of various specialties have variable degrees of awareness of this lymphoma, its diagnosis, and therapy. Because the optimal management of this lymphoma and the suggested standard of care has been established in the last few years, it is expected that some patients in this series did not receive an optimal therapy and management.

We expect that the recognition of the BIA-ALCL Registry in Colombia will continue its educational role, leading the efforts to prospectively identify patients through the interdisciplinary group with the support of government authorities. We believe that this enterprise will help affected patients to benefit from access to a supportive health care system. We envision that we, with the consent of affected patients, will prospectively accrue pathologic specimens for sophisticated testing to unveil the science underneath this lymphoma, using the advantages of modern molecular biology, which will allow a better global understanding of BIA-ALCL.

CONCLUSIONS

Colombia has a high volume of breast surgery involving breast implants. Therefore, we developed a registry for the surveillance and monitoring of BIA-ALCL. This Colombian Registry of BIA-ALCL has identified 18 cases, including the first case of a death in our country. All patients were following cosmetic augmentations; several different manufacturers of textured implants were represented. A high proportion of advanced disease may be a consequence of delayed presentation, lack of disease awareness, and timely access to tertiary cancer centers for diagnosis and treatment. Therefore, joint multidisciplinary strategies are required to strengthen surveillance and monitoring of BIA-ALCL among the major breast implant markets in the world.

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