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SYSTEMATIC REVIEW: ANAPLASTIC LARGE CELL LYMPHOMA FOLLOWING BREAST IMPLANT SURGERY

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ABSTRACT

Introduction: BIA-ALCL, a T-cell lymphoma associated with breast implants, poses a growing medical challenge despite its relatively low occurrence, due to the increasing use of implants for cosmetic and reconstructive purposes. Our objective is to review the incidence, characteristics of patients, implant types, management, and outcome of BIA-ALCL.

Methods: Pubmed and Science Direct databases were searched to identify case series and observational research. A systematic review was conducted by looking up the keywords "breast implant" and "anaplastic large cell lymphoma".

Results: 11 relevant articles were assessed. A total of 353 BIA-ALCL cases have been reported. The mean age at diagnosis was 59.6 years. More than half (53.26%) of the reasons for the breast implants in BIA-ALCL patients were cosmetic. The mean time from breast implant placement to diagnosis was 9.99 years. The majority (71.39%) of documented BIA-ALCL cases have been associated with textured devices. BIA-ALCL patients mainly presented with seroma (54.67%). Outcomes included remission (71%), death because of the disease (4.25%), and recurrence (3.96%) with a mean time of duration of follow-up was 2.53 years.

Conclusion: BIA-ALCL is rare cancer in some patients with breast implants but is increasing in incidence largely due to consistent and long-term follow-up. It is important for physicians involved in the care of patients with breast implants to be aware of BIA-ALCL and do routine breast exams.

Highlights:

1. BIA-ALCL, a T-cell lymphoma associated with breast implants, is posing a growing medical challenge due to the increasing use of implants for cosmetic and reconstructive purposes.
2. The majority of BIA-ALCL cases were associated with cosmetic reasons for breast implants, and textured implants were predominantly implicated.

INTRODUCTION

Breast implantation is a common surgical procedure for breast augmentation or reconstruction of the breast following a mastectomy. The first pair of silicone gel-filled implants were inserted in 1962. Breast implants, like any other implanted foreign body, come with risks. The first documented case of BIA-ALCL was discovered in 1997 by

Keech and Creech when they observed an association between BIA-ALCL and a saline-filled breast implant. Since then, there has been an expanding awareness of this substance[1]. Implants can be categorized into saline-filled, silicone-filled, or mixed, with smooth or textured[2]. The Food and Drug Administration (FDA) announced in 2011 that there could be a connection between breast implants and the development of ALCL. In March 2018, the FDA stated BIA-ALCL is an uncommon but highly treatable disease, emphasizing textured implants as the cause of most cases[3]. The prognosis for BIA-ALCL is excellent, with a low risk of death compared to other malignancies[4]. Because this disease can be treated and has a good prognosis, early detection is important.

ALCL itself is a rare disease with only 2 percent of all newly diagnosed non-Hodgkin lymphomas worldwide[5]. Primary lymphoma of the breast takes up 0.4 to 0.5 percent of all breast malignancies and approximately 1 to 2 percent of all extra-nodal lymphomas, almost all of them of less aggressive B-cell origin[6]. Although BIA-ALCL develops around breast implants, BIA-ALCL is not considered breast cancer but a malignancy of the immune system. BIA-ALCL is a CD30-positive, anaplastic lymphoma kinase-negative T-cell lymphoma. BIA-ALCL is found mostly in the scar tissue and fluid around the implant, although it can spread systemically in some cases[7].

Despite the infrequency of this disease, there has been a growing number of case series and case reports published. Our study aims to systematically review the incidence, implant characteristics, clinical presentations, treatments, and outcomes of this disease.

METHODS

Data searching strategy

This systematic review was done according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement and Cochrane Handbook for Systematic Reviews of Interventions (S1 Table)[8,9]. We searched PubMed and Science Direct databases to identify all cases of BIA-ALCL reported since 10 years ago. The search start date was March 10, 2021, to March 17, 2021. We used the following keywords: "(((Anaplastic large cell lymphoma [MeSH Terms])) AND ((Breast implant [MeSH Terms])) OR (Breast Implant surgery [MeSH Terms]))".

Eligibility criteria

Search results were categorized as research (epidemiologic studies or scientific articles) and non-research (case reports or case series) articles from peer-reviewed journals, reviews, letters to the editor, conference abstracts, and unpublished manuscripts. Only human-based topics and articles written in English were considered. The inclusion criteria were observational study design and case series, full-text in English, and study in the last 10 years. The exclusion criteria were case report/ systematic review/ meta-analysis.

Data extraction and quality assessment

Criteria for including a case required that at least some additional information other than diagnosis was available (e.g., history, symptoms, follow-up). Data elements abstracted included information about patient demographics, medical history, implant characteristics, presenting symptoms, diagnosis and staging, treatment, and patient outcomes. Detailed summary tables were

created, which contained frequencies, means, and ranges for each abstracted variable, as applicable. To minimize the risk of bias, quality assessment of eligible studies was performed through Newcastle-Ottawa Scale (NOS) for observational study[10].

RESULTS

Literature Search

In total, 592 titles were returned by the literature search. Of these, 11 articles were selected for review presenting 353 new cases of BIA-ALCL. Three (27.2 percent) were case series and eight (72.73 percent) were observational studies. (Figure 1).

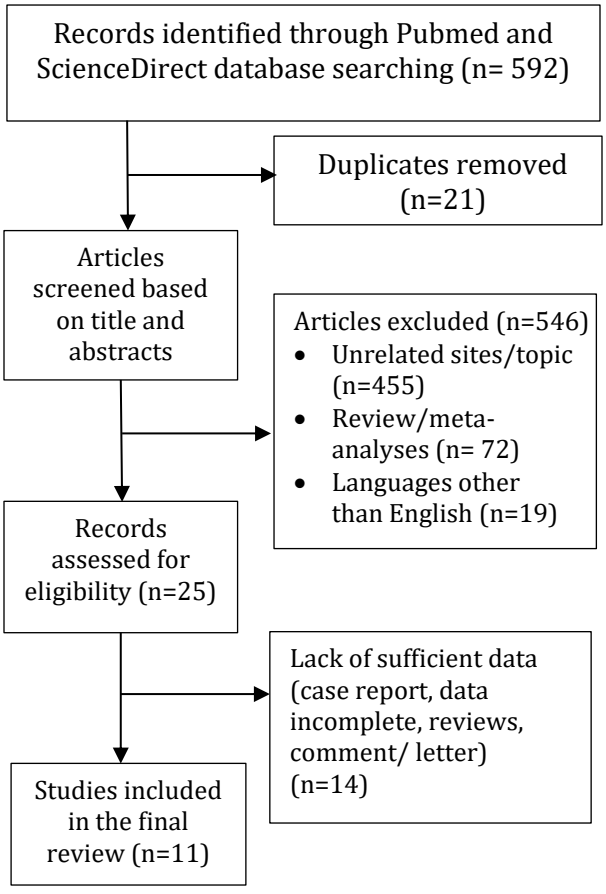

Figure 1. Literature flow of published BIA-ALCL articles

Table 1. Summary of Studied Included in Final Review

Study (risk of bias assessment)	Country (Year)	Design	BIA-ALCL cases
Cordeiro et al.[11] (NOS score: 7/9)	New York, USA (2020)	Prospective Cohort	10
Collins et al.[12] (NOS score: 8/9)	Texas, USA (2019)	Retrospective	39
Lamaris et al.[13] (NOS score: 9/9)	Toronto, Canada (2019)	Retrospective	18
Doren et al.[14] (NOS score: 8/9)	Texas, USA (2017)	Retrospective	100
Dashevsky et al.[15] (NOS score: 7/9)	New York, USA (2018)	Cohort	11
Nelson et al.[16] (NOS score: 9/9)	New York, USA (2020(	Cohort	11
Campanale et al.[17] (NOS score: 9/9)	Rome, Italia (2020)	Case series	46
Loch-Wilkinson et al.[18] (NOS score: 9/9)	Australia (2017)	Cohort	55
Johnson et al.[19] (NOS score: 8/9)	United Kingdom (2017)	Case series	18
Aladily et al.[20] (NOS score: 8/9)	Texas, USA (2012)	Case series	13
De Boer et al.[21] (NOS score: 9/9)	Amsterdam, Netherland (2018)	Case-control	32

*NOS: Newcastle-Ottawa Scale

Patient Characteristics

Characteristics of the patients, information on their medical history, and data on their implant types are summarized in Table 2. In our systematic review, the estimated mean age at BIA-ALCL diagnosis was 59.6 (range 28 to 87) years. Of 353 women who developed BIA-ALCL, 188 (53.26 percent) underwent the original implant surgery for cosmetic augmentation, and 161 (45.61 percent) for reconstruction after cancer surgery or prophylaxis of breast cancer. Seven (1.98 percent) patients reported no data. 188 (53.26 percent) patients had a history of cancer.

Implant Characteristics

Data were not consistently reported on the placement of the implant or the size, surface, and implant covering. Almost all of the cases had no data about implant placement (i.e., sub glandular, subpectoral, or submuscular). Of the 261 cases with available data, 251 (96.1 percent) of the implants were reported to have a textured surface. The implant covering was also rarely reported. Of the 20 (5.66 percent) that were reported, ten reported a silicone covering, and ten reported a polyurethane foam covering. The type of implants used among the BIA-ALCL cases was saline in 30 (8.5 percent) and silicone in 133 (37.39 percent) (26.1 percent did not report implant type). Two hundred-one of the 353 BIA-ALCL cases (56.04 percent) had data about the implant manufacturer/model. Of these 201, 95 (26.91 percent of 54) reported Allergan, one (2 percent) reported Allergan/Inamed/McGhan, 8 (2.27 percent) reported Nagor, 14 (3.97 percent) reported Silimed, five (1.42percent) reported Mentor, 47 (13.31 percent) reported Salt Loss, four (1.13 percent) reported PIP, five (1.42 percent) reported Negative Imprint, and one (0.28 percent) reported Surgitek. Of note, not all manufacturers labeled their implants in the past; thus, when not reported, it is unknown whether this was simply not reported by choice or not reported because the implant was not labeled.

Table 2. Characteristics of BIA-ALCL Cases

	Total (%)*
No.	353
Age at diagnosis, yr	
Mean	59.6
Range	29-87
Affected breast	
Unilateral	
Left	34 (9.63)
Right	32 (9.06)
Unknown	74 (20.96)
Bilateral	77 (21.81)
Not reported	136 (38.53)
Reason for initial implant	
Cosmetic	188 (53.26)
Reconstruction	161 (45.61)
Not reported	7 (1.98)
History of cancer	
Yes	202 (57.22)
No	151 (42.78)
Times between implant and BIA-ALCL diagnostic (yr)	
Mean	9.99
Range	0.2-27
Surface	
Smooth	10 (2.83)
Textured	251 (71.39)
Not reported	92 (26.1)
Covering	
Silicone	10 (2.83)
Polyurethane	10 (2.83)
Not reported	312 (88.39)
Type of implant filling	

Silicone	132 (37.39)
Saline	30 (8.50)
Both	2 (0.57)
Not reported	189 (53.54)
Manufacturer/ model	
Allergan/Inamed/McGhan	95 (26.91)
Nagor	8 (2.27)
Silimed	14 (3.97)
Mentor Silicone	5 (1.42)
Salt Loss	47 (13.31)
Poly Implant Prothese	4 (1.13)
Negative Imprint	5 (1.42)
Surgitek	1 (0.28)
Not reported	152 (43.06)

Case Presentation

More than half (193; 54.67 percent) of 353 patients reported having seroma/ effusion around the implant. Fifty-eight of 353 BIA-ALCL cases (16.43 percent) reported data indicating that the patient had a palpable breast mass on presentation (Table 3). Sizes of the mass were not reported. The presence of lymph node involvement was addressed in 27 (7.6 percent) patients. Duration of symptoms was rarely noted.

Diagnosis and Staging of the Disease

The mean time to diagnosis was 9.99 (range, 0.2 to 27 years). By the *National Comprehensive Cancer Network* Consensus Guidelines for Breast Diagnosis and Management of BIA-ALCL, at the time of diagnosis, 51 patients (14.44 percent) were in stage IA, 1 (0.28 percent) were in stage IB, three (0.85percent) were in stage IC, 17 (4.82 percent) were in stage IIA, three (0.85 percent) were in stage IIB; eleven cases (3.12 percent) was in stage III; seven (1.09 percent) were in stage IV; and nine cases (2.25 percent) were not reported. Non-Hodgkin lymphoma is traditionally staged utilizing the Lugano modification of the Ann Arbor staging system. Stage IE disease is limited to a single extranodal (E) site such as the breast or implant capsule, whereas stage IIE disease is defined as an extranodal disease with spread to or involvement of local lymph nodes. 29 cases (8.22 percent) were in stage IE and 21 cases (6.23 percent) were in stage IIE.

Table 3. Clinical Course of Patients with BIA-ALCL

	Value (%)
Total subject	353
Seroma	
Yes	193 (54.67)
No	60 (16.98)
Not reported	100 (28.39)
Mass	
Yes	58 (16.43)
No	195 (55.24)
Not reported	100 (28.39)
A lymph node investigation performed	
Yes	27 (7.6)
No	226 (64.02)
Not reported	100 (28.39)
Stage (Ann Arbor)	
IE	29 (8.22)
IIE	21 (6.23)
IV	1 (0.28)
Not reported	302 (85.56)
Stage (TNM)	
IA	51 (14.44)
IB	1 (0.28)
IC	3 (0.85)
IIA	17 (4.82)
IIB	3 (0.85)
III	11 (3.12)
IV	7 (1.09)
Not Reported	9 (2.55)

TNM, tumor, node, metastasis. Staging IA = T1N0M0; IB=T2N0M0; IC= T3N0M0; IIA= T4N0M0; IIB=T1=3N1M0; III= T4N1-2M0; IV= TanyNanyM1

Surgical Treatments and Adjuvant Therapies

The affected implant was reported as removed in 253 of the 353 reported cases of BIA-ALCL (71.67 percent) (Table 3). The remaining 100 cases (28.39 percent) provided no data regarding removal. Of the 353 cases, 110 (31.16 percent) were reported to have surgical removal of the contralateral implants. In no cases were the implants reported to be left in place on the affected side. However, most reports (58.36 percent) gave no information about the status of the contralateral implant.

Of all of the 353 cases, 89 (25.21 percent) received chemotherapy, although information about chemotherapy was not reported for 28.3 percent of the cases. 175 (49.58 percent) received no chemotherapy. When chemotherapy regimens were reported, the regimens were noted to consist mostly of cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone (plus/minus other chemotherapeutic agents). Six cases (1.7 percent) received neoadjuvant chemotherapy. Thirty-nine (11.05 percent) received radiation therapy, not report the location of radiation in either the chest wall or axillary or other places. 194 (54.96 percent) did not receive radiation therapy. Information on radiation therapy was not reported for 100 (28.33 percent). Twelve cases (3.4 percent) received a stem cell transplant for treatment of their BIA-ALCL.

Table 4. Treatment of Patients with BIA-ALCL

	Value (%)
Surgical removal of the affected implant	
Yes	253 (71.67)
No	0
Not reported	100 (28.39)
Radiation therapy	
Yes	39 (11.05)
No	194 (54.96)
Not reported	100 (28.33)
Chemotherapy/other	
Yes	89 (25.21)
Neoadjuvant	6 (1.70)
Adjuvant	
CHOP	19 (5.38)
CHOEP	4 (1.13)
CHOEP+DHAP/DX/BRX	5 (1.14)
Not reported	55 (15.58)
No	175 (49.58)
Not reported	100 (28.33)
Stem cell transplant	
Yes	12 (3.4)
No	241 (68.37)
Not reported	100 (28.33)
Clinical follow-up reported	
Yes	216 (61.19)
No	137 (38.81)
Duration of follow-up (years)	
Mean	2,53
Range	0.1-12
Outcome	
DOD	15 (4.25)
DOUD	7 (1.98)
CR	86 (24.36)
Recurrence	14 (3.96)
Not reported	231(5.44)

CHOP, cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone; ESHAP, etoposide, methylprednisolone, cytarabine, and cisplatin; ICE, ifosfamide, carboplatin, and etoposide; ABVD, Adriamycin, bleomycin, vinblastine, and dacarbazine. DOD: Death of the disease, DOUD: Death of the unrelated disease, CR: Complete remission

*Totals may not sum to 100% because of rounding.

Outcome

Some sort of clinical follow-up was reported for 216 cases (61.19 percent), although the frequency of follow-up was never reported. When reported, the mean duration of follow-up was 2.53 years (range, 0.1 to 12 years). Of the 216 cases with follow-up data, 86 (24.36) had complete remission, 14 (3.96 percent) had a recurrence, 15 (4.25

percent) died as a result of the disease, 7 (1.98 percent) died as a result of underlying disease, 7 (1.98) and 231 (65.44 percent) did not have information regarding follow up.

DISCUSSIONS

BIA-ALCL is a rare type of lymphoma that was initially described in 1997[1]. The FDA has received more than 300 records of BIA-ALCL (medical device reports of BIA-ALCL), Our systematic review identified 353 cases of BIA-ALCL occurring in women with breast implants. The chance to develop BIA-ALCL among patients with breast implants is low and, according to a study in the Netherlands, the incidence is 1 in 500,000 women who have received breast implants[22]. Breast implants are used by 5 to 10 million women worldwide, and the rates of breast augmentation and implant-based breast reconstruction are rising every year. Eighty-three percent of breast reconstructions in the United States in 2010 were implant-based[23].

A rise in the number of BIA-ALCL cases diagnosed was expected. In our study, above half of the patients had cosmetic reasons for their initial implant. This is significant because cosmetic patients frequently do not follow up with their plastic surgeon after 1 post-operative year, although this paradigm is changing among some practitioners. Patients with breast cancer commonly see their breast surgeon or medical oncologist for follow-up far after the first year of the reconstruction surgery. Furthermore, if a woman is seen at the emergency department or by a general practitioner with breast problems, she is often first referred to a general surgeon or breast surgeon even if she has breast implants. Since these practitioners may be unaware of the diagnosis of BIA-ALCL due to a lack of clear symptoms, there is a risk of delay or misdiagnosis. They may be unfamiliar with the immunochemistry stains that must be requested, as well as the type of implant used. Most of the literature that was previously published has been in plastic surgery journals; therefore, it is needed to spread the information about this diagnosis to other medical and surgical specialties that have a higher chance to come into contact with these patients first. Many patients are also unaware of this condition [24].

In our study, a majority (71.39%) of the BIA-ALCL cases had textured surface implants. Although the textured implant surface adheres to the fibrous capsule naturally produced by the body, which helps to maintain implant position and location; on the contrary, smooth implants are more mobile. A hypothesis suggested that the texture of the implants was related to a greater number of cases, those that were more aggressively texturized and had a denser biofilm, in which the predisposed patients would be more likely to develop inflammatory and lymphoma formations. In a study by Loch-Wilkinson et al reviewing the cases of BIA-ALCL in Australia and New Zealand, the authors noted that higher surface area textured implants significantly increase the risk for the development of BIA-ALCL.[18] Prior work by Hu et al found that textured implants retain up to 72 times more bacteria on the implant surface compared to smooth implants due to their increased surface area[25-26]. Hu et al also discovered that textured, rather than smooth breast implants, elicited a stronger immune response with a higher proportion of T cell lymphocytes, rather than B cells. This T cell hyperplasia likely devolves into BIA-ALCL, a T cell lymphoma subtype. As there are likely many other contributory factors, further research is needed to determine whether there is a causal relationship between implant type and BIA-ALCL. The anaplastic gigantic cell lymphoma in breast implants is associated with a chronic immune response, which is primarily consisting of lymphocyte cells, T CD4 and CD30. There is the possibility that

the trigger is bacteria, a super-antigen from staphylococcus, which triggers CD4 cell proliferation in the lymphoma cutaneous, specifically lymphoma CD30. Interestingly, the ALCL associated with implants is very similar to cutaneous benign lymphoma[27]. A load of bacteria increases the biofilm over the texturized structures, particularly in the most aggressive textures or macro-textures. Deva discovered that bacteria in the biofilm interface showed a possible connection between the number of bacteria and the number of lymphocytes. In some studies, there was a rise in the dimension of the biofilm, and the bacteria found has been negatively compared to the capsular contracture that was positive. Any chronic inflammatory process can trigger a lymphoproliferative disorder with a potential relationship with lymphoma[28].

More than half (54%) of BIA-ALCL in our study had a fluid collection arising in the peri-implant fibrous capsule (seroma). There were just a few patients who had a mass. Inflammatory cells confined to the peri-implant capsule, according to Laurent et al, may represent an in-situ disease, while those with an associated mass may have a more advanced form, with infiltration of adjacent tissues beyond the capsule[29]. The majority of patients who present with an effusion around the implant but no tumor mass achieve full remission and have a good prognosis. Patients with a tumor mass associated with the fibrous capsule make up a smaller group of patients that are more likely to have clinically aggressive disease. We suggest that patients without a tumor may benefit from conservative treatment, perhaps implant removal with capsulectomy alone, and patients with a tumor mass may require implant removal as well as systemic therapy, which is still being identified[30].

From the available guidelines that we found, one of the most used is *National Comprehensive Cancer Network (*NCCN). They recommend implant removal, complete capsulectomies, and excision of suspicious lymph nodes. They also recommend the removal of the contralateral breast implant, and our study found that 110 patients out of 253 patients that received surgical removal also had the contralateral implant surgically removed. In our study, the most used adjuvant therapy was chemotherapy (which is 25.21%). However, we found no specific trial in the guidelines to guide the management of patients with advanced BIA-ALCL. But we found that radiotherapy is suggested for patients with local residual disease, positive margins, or unresectable disease with chest wall invasion. While systemic therapy, such as chemotherapy, is suggested for patients with Lugano / Ann Arbor stage II-IV or MDA TNM stage IIB-IV disease and de-novo ALK-negative systemic ALCL[31].

We identified only a small number (4.52%) of deaths of the disease, but obtaining more detailed information on such patients, and ensuring long-term follow-up for all BIA-ALCL patients, would allow for more effective identification of at-risk patients. It is extremely important to understand risk factors that cause death (e.g., stage at presentation, history of lymphoma, or lymphoma-like conditions), even though BIA-ALCL is thought to have a benign course in general. This allows clinicians to raise suspicion for aggressive disease early on and may suggest the need for very close follow-up, systemic chemotherapy, and/ or radiation therapy[31].

We note that there are still very few cases of BIA-ALCL reported in the literature, which makes the identification of risk factors for optimal management of BIA-ALCL difficult. The case reports rarely report the information of complete diagnostic or clinical presentation. Sometimes, these data are not available to reporting clinicians, such as when

the patient is lost to follow-up or changes their care to another provider. Given that case reports and case series are often written by clinicians with varying backgrounds, and thus differing areas of interest, perhaps a better approach to gather systematic information on this entity would be to start a disease registry. We recommend that manufacturers and regulators collaborate if possible to share data about cases of BIA-ALCL and/or implant registries. This would enable the collection of a larger number of cases and eliminate the possibility of duplicate cases being reported in different registries[24].

In all chronic seromas related to breast implants, the presence and possibility of BIA-ALCL diagnosis should be taken into account. It is advisable to take an immunohistochemistry test and seek assistance from a pathologist who is familiar with the diagnosis of lymphoma. There is no universal treatment. Treatment of this disease involves a multidisciplinary team. It must be evaluated by bilateral surgical removal of the capsule with the removal of the implants. New treatments such as Brentuximab can be helpful in advanced cases [32].

There are still few review studies that focus on BIA-ALCL. Therefore, this review gives the newest review of BIA-ALCL. However, this study also has limitations. The data consisted of clinical case series/retrospective studies that were not homogeneous, which did not enable a statistical analysis to be performed to determine the potential associations.

CONCLUSION

BIA-ALCL case is higher in patients with textured surfaces. The most common clinical course is seroma. We identified only a small number of deaths of the disease, but obtaining detailed information and ensuring long-term follow-up will give us the best result. It is important for physicians involved in the care of patients with breast implants to be aware of BIA-ALCL and for the breast implant patient to do routine breast exams.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest regarding the publication of this study.

FUNDING DISCLOSURE

No funding disclosure statement was provided for this study.

AUTHOR CONTRIBUTION

KE reviewed all relevant references to identify articles containing case information, data extraction, and analysis, and wrote the manuscript. For each identified case, two clinicians were reviewed by LBA and RSL. BSN was study design, supervised the research process, and reviewed and edited the manuscript. independently recorded all available case-based data and then compared and reconciled their data.

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