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SPECIAL UPDATE: The epidemiology of Breast Implant Associated Large Cell Lymphoma in Australia and New Zealand confirms the highest risk for grade 4 surface breast implants

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Abstract

Background: The epidemiology and implant specific risk for BIA-ALCL has been previously reported for Australia and New Zealand. We now present updated data and risk assessment since our last report.

Methods: New cases in Australia and New Zealand were identified and analyzed. Updated sales data from three leading breast implant manufacturers (i.e., Mentor, Allergan, and Silimed) were secured to estimate implant-specific risk.

Results: A total of 26 new cases of ALCL were diagnosed between January 2017 to April 2018 increasing the total number of confirmed cases in Australia and New Zealand to 81. This represents a 47% increase in number of reported cases over this time period. The mean age and time to development remains unchanged. The implant specific risk has increased for Silimed Polyurethane (23.4 times higher) as compared with Biocell, which has remained relatively static (16.5 times higher) compared with Siltex implants.

Conclusions: The number of confirmed cases of BIA-ALCL in Australia and New Zealand continues to rise. The implant specific risk has now changed to reflect a strong link to implant surface area/roughness as a major association with this cancer.

Introduction

Public awareness of Breast implant associated anaplastic large cell lymphoma (BIA-ALCL) , a T cell non-Hodgkins lymphoma and its relationship to textured breast implants, is growing[1,2]. The delineation of an accurate risk of developing BIA-ALCL has, to date, been difficult to characterize due to the lack of good prospective follow up data and outcomes following breast implant surgery for both reconstructive and aesthetic surgery. A wide range in incidence and risk has been subsequently reported depending on the likely true numerator (number of cases in a given population) and denominator (number of implants being utilized in a given population over time). We have previously published the Australia and New Zealand epidemiology of BIA-ALCL and estimated implant specific risk using capture of known cases as numerator and sales of specific textured implants over a period of time as the denominator[3]. Whilst there are limitations with this method, a number of other studies have concurred with this broad level of risk[4-6].

We have continued to prospectively collect data on new cases through a cooperative alliance of breast surgeons, plastic surgeons, registry scientists and hematologists throughout Australia and New Zealand. Both Mentor (Johnson & Johnson) and Allergan provided updated sales data and since the sales of Silimed Polyurethane implants remain suspended in Australia, we utilized the previous sales numbers for this implant to recalculate implant specific risk for all three implant types. We also applied the recently described surface area/roughness grading classification[7] to more clearly delineate risk of BIA-ALCL using these parameters.

Methods

These have been previously reported[3]. Implants were graded using combined surface area/roughness categories as reported by Jones et al[7] (see Figure 1).

Results

Patient and implant characteristics

There have been a further 22 pathologically confirmed cases in Australia (up from 46) and 4 confirmed in New Zealand (up from 9) since our last count in December 2016, representing a 47% increase in reported cases with a rise from 55 to 81. Sixteen patients had exposure to multiple implants (20%) whilst the remaining 65 had single-implant exposure. The mean age and mean time of exposure remain similar to our previous findings (48 years, range 22,4-78.5, 7.58 years, range 0.5-25.0). Fifty-nine patients (73%) had implants for cosmetic indication whilst 22 (27%) had implants for breast reconstruction following cancer. Figure 2 shows the rise in cases in Australia and New Zealand since the index case in 2007. The time period for reporting in 2017/8 is not complete.

Table 1 summarizes the implant type and surface grade of the 110 implants utilized in the 81 patients. 78.9% of implants were either surface grade 3 or 4, based on our recently published implant classification system[7], indicating a predominance of high surface area/surface roughness implants in this series. All patients had exposure to textured (surface grade 2,3,4) devices with no cases reporting development of BIA-ALCL following use of only smooth (surface grade 1) devices to date. All patients with exposure to smooth (surface grade 1) devices had subsequent exposure to textured (surface grade 2,3,4) implants. Comparison with implant types from our previous publication[3] is included.

Presentation, staging and survival

The commonest presentation of BIA-ALCL remains unilateral late seroma observed in 84% of patients. Table 2 summarizes the clinico-pathological staging of patients in our series with comparison to our previous published data[3]. A further 62.9% of patients presented stage 1a negative disease. This corresponds to disease limited to the effusion on cytological diagnosis but with completely negative histopathology of the capsule and residual seroma fluid at time of oncological capsulectomy. A further 16.0% of patients present with stage 1a positive disease – findings of a lining of BIA-ALCL tumor cells on the inner aspect of the capsule often associated with high rates of apoptosis. We have four patients that presented with Stage 2a disease with locally advanced mass disease (T4). In 3 of these patients, there was a significant delay in diagnosis. In 1 patient, the diagnosis was made incidentally at the time of surgery. We have not had any further deaths to report from BIA-ALCL. We also noted geographic clusters of BIA-ALCL (n=2-8) arising from single surgeon practices.

Mean duration of exposure to varying implant types are reported in table 1 and were not found to be significantly different.

Implant related risk

The Odds Ratio (OR) for developing BIA-ALCL for Biocell implants compared to Siltex has risen to 16.52 (95 percent CI, 3.60 – 293.05, $p<0.0001$). The OR for developing BIA-ALCL for Polyurethane (Silimed) implants compared to Siltex was 23.4 (95 percent CI, 4.53-428.59, $p<0.0001$).

Figure 3 shows the Kaplan Meier projections of cases confirming a rise in the risk associated with Grade 4 surface implants as we predicted from our previous analysis.

Table 3 summarizes implant specific risk, expressed as cases of BIA-ALCL per number of implantations, for the three implant types with known sales data. Silimed polyurethane (Grade 4 surface) is now associated with the highest risk of developing BIA-ALCL of 1 case for every 2832 implants utilized (range 1583-5673). Nagor has continued to deny access to their sales data to allow a risk calculation. Surgitek and PIP implants have been discontinued from sale.

Discussion

Our study has demonstrated a substantial rise in the number of reported BIA-ALCL cases in Australia and New Zealand in the 16 months since our last report. The increased number could represent a combination of a true rise in incidence and/or an increased level of detection with raised awareness of this disease. Fortunately, in spite of the increased numbers, the majority of these patients have presented with early stage (1A) disease indicating that the process of early diagnosis and facilitated treatment is working. Stage 1A disease is indolent and curable through surgery alone and this may explain why we have had no further deaths from BIA-ALCL since our last report. The importance of early detection and treatment cannot be more strongly emphasized. Three of the four patients that presented with advanced disease experienced a delay in diagnosis, which may have contributed to the risk of spread. The introduction of routine surveillance programs of all women with breast implants should also be considered.

Patients are diagnosed from a pre-operative seroma aspiration and appropriate cytology to detect large anaplastic cells, flow cytometry to detect aberrant T-cells and immunohistochemistry for T-Cell markers (CD30 positive and ALK negative)[1]. Our series shows that the majority of patients present with Stage 1a (effusion-limited) disease which is both indolent and eminently curable. We have further categorized

effusion-limited disease as negative – with subsequent absence of BIA-ALCL in histological examination and positive – with a few tumor cells loosely adherent to the inner lining of the implant capsule. The absence of tumor cells in subsequent pathological testing does not represent regression or spontaneous resolution, as has been erroneously suggested but rather, a lowering of the tumor cell burden following drainage of the malignant seroma[8]. These patients accounted for around 80% of BIA-ALCL in our series. This proportion is now being echoed through other clinical series[4]. The higher predominance of more advanced disease in some series reported from the United States may reflect the failure to properly identify effusion-limited disease as a result of variable insurance coverage and/or fear of litigation.

The progression from effusion-limited disease to more invasive disease is still not clear and is the subject of further study. It is likely that in the majority of cases, the disease is held at this early stage until further mutational load and/or antigenic drivers transform the malignant phenotype into a more aggressive tumor. We are currently investigating the genetic differences in both tumor and germline to look for a genetic or HLA "gate" that permits disease progression. The relationship between early stage BIA-ALCL and benign late inflammatory seroma also requires closer study. Patterns of inflammatory cytokine release, clonality of lymphocyte response and accumulation of genetic mutations may well allow us to delineate between established malignancy versus lympho-proliferation. To that end, stage 1a disease should be now re-classified as effusion-limited and be recognized for its indolent nature. To our knowledge, there are no patients with effusion-limited disease that have recurred after adequate surgical treatment.

Analysis of implant type combined with updated sales data for 3 implant types have now confirmed that the highest risk for BIA-ALCL in Australia and New Zealand is for implants with a Grade 4 surface[7].

Our methods, which were previously reported, relied on industry sales data for our denominator and were duplicated for both single and multiple implant exposure. The limitations of this method have been previously outlined but in the absence of any prospective registry data, represents the best way to ascertain implant specific risk. We have now shown that surface grade 4, which carries the highest surface area and surface roughness, and has been shown to potentiate the growth of both gram positive and gram negative bacteria[7]. The grade 4 surface (Silimed PU) has been demonstrated to show significantly higher rates of bacterial growth (and associated T cell activation) in both animal models and human series of capsular contracture[9,10].

Polyurethane coatings for breast implants were first introduced in 1968 with the "Natural Y" implant, incorporating a 1.2-2mm polyurethane foam coating on the outer surface[11,12]. The aim of this novel texture was to prevent organized alignment of myofibroblasts, thereby reducing the risk of capsular contracture[11]. After a period of use in patients, a specific association between polyurethane and the carcinogen 2,4-toluendiamine (TDA) was reported[13,14], leading to a withdrawal of these implants in the USA. Further studies have confirmed that levels of TDA are equivalent to occupational exposure and are unlikely to cause a significant risk to patients[15,16]. The use of polyurethane implants outside of the US has continued and there is some clinical evidence to support its effectiveness in reducing capsular contracture[17]. Variable technique and length of follow up, however, impact on this claim. A recent long term 30 year study has shown that the rates of capsular contracture with Polyurethane implants, however, rise significantly after 10 years, coincident with the

degradation and phagocytosis of the polyurethane coating[18]. The benefits vs. risk of these coatings need to prospectively studied to generate better clinical efficacy and safety data, especially with the higher risk reported on BIA-ALCL now associated with Silimed PU implants in our series.

We do not have access to sales data from other grade 4 surface implants manufactured by Surgitek (now discontinued) and Polytech. The differential number of cases in our series between these grade 4 implants and Silimed PU may be reflective of the fact that Silimed implants have been utilized in Australia and New Zealand for the longest period of time and in the highest numbers to date. Further longitudinal follow up of patients with PU implants of any type will determine if the risk is transferable across to other grade 4 implant surfaces. Interestingly, the first case of BIA-ALCL associated with Polytech PU (Grade 4) implant had only been implanted for 4.5 years prior to her presentation. We also are unable to obtain sales numbers from PIP implants, which were discontinued and Nagor continues to deny access to their Australian/New Zealand sales data in spite of repeated requests. For smooth implants, we do not have access to sales data for these devices and these patients all had subsequent replacement with textured implants prior to developing BIA-ALCL. To date, we are not aware of any cases that have arisen from exposure to smooth devices in isolation, which justifies our focus on risk calculation for textured devices alone. The cluster pattern of incidence now observed in both this and other series[4,6] and the increasing evidence of microbiome induction and potentiation of cancer[19-21] do suggest a role for infection in pathogenesis. In a very close analogue of BIA-ALCL, primary cutaneous ALCL (pcALCL) has also been shown to be primarily indolent with a long latent period, mirroring the spectrum of disease and progression we have shown in these data. In recent research, the identification of bacterial antigens as a

likely driver of this disease[22,23] also further supports the possible role of bacteria in the genesis of BIA-ALCL[24]. Further work on the mechanisms of bacterial antigenic interaction with both tumor cells and the host adaptive immune response are underway and will provide further clues as to pathogenesis of this disease, in time. Other sources of inflammation (e.g. particulates, friction) have been put forward as alternatives for initiating the activation and transformation of lymphocytes[8]. Webb et al have shown that when an adhesive copolymer was applied and removed to implant shells *in* vitro, that the Allergan implant had the highest shedding of particulate matter[25]. This study did not examine PU shells and has not justified the *in vivo* significance of their methods.

Whilst the link between physical/mutagen induced inflammation and carcinogenesis has been well studied[26-28], the link between inflammation derived from the innate immune response (e.g. macrophages, neutrophils, eosinophils) and activation and transformation of T lymphocytes into lymphoma has not been made. Apart from transformation induced by virus infection and direct oncogene activation (such as with HTLV3 and EBV), all T cell lymphomas have been driven by the interaction of a biological antigen (bacteria, gluten, autoantigens) with cell surface receptors on the target T cell[29]. This interaction pushes T cell differentiation towards a malignant phenotype. We do concede that generalized inflammation via the innate pathway, however, could theoretically raise the level of cellular proliferation, cytokine release and contribute to amplification of a direct lymphomagenic stimulus through a biological antigenic signal. Alternatively, accumulation of mutations from proliferation may provide a pathway to lymphomagenesis, although this mechanism has yet to be elucidated in long term *in vitro* and *in vivo* studies of T cell lymphomagenesis. Further investigation is needed to build biological plausibility of

lymphomagenesis through innate inflammation alone in the absence of an adaptive immune trigger.

The risk for grade 3 and 4 surface implants needs to be clearly articulated. It is no longer valid to quote overall risk for all breast implants. The use of the terms "micro, macro and nano" texture should also be phased out in favor of the numeric classification, based on objective measurement[7]. These data show that BIA-ALCL is essentially a disease associated with grade 3 and 4 breast implant surfaces. The higher level of risk for these implants has also been independently confirmed by other series[4-6].

We have shown the importance of active cooperation, notification and transparent reporting of new cases as a means of clarifying the epidemiology, disease spectrum and risk to patients. It has also allowed us to build a considerable tissue bank to study the biology and initiating factors associated with BIA-ALCL. Collaboration has been key to the sharing of data between our regulator, research group, registry scientists and most clinical groups (including Plastic Surgeons, Breast Surgeons and Hematology/Oncology). We concede that there may be incomplete capture of BIA-ALCL cases by our network. We have on a number of occasions, been able to access delinked implantation data through cross checking with regulators, both national and international. Going forward, mandatory reporting of this disease should be considered so as to ensure that disease capture is both accurate and timely.

Ultimately, it is the maturing of breast implant registries that will provide us with good prospective data[2,30,31]. This will take time and whilst we wait for this to develop, we will continue to report our findings in 12-16 month intervals to ensure that risk is further delineated. We submit that the infrastructure of disease capture and analysis that we have been able to achieve in Australia & New Zealand should serve as the

preferred template for how to study BIA-ALCL worldwide until such time as good longitudinal prospective data are available.

Conclusions

We expect the number of reported cases of BIA-ALCL to continue to rise in Australia and New Zealand. The predominance of effusion-limited disease as the major presentation of BIA-ALCL with good cure rates in our series further emphasizes the importance of early detection and treatment. The findings of significantly higher implant specific risk for Grade 3 and 4 implant surfaces will allow better communication of risk to patients and serve to aid the surgeon in choice of implant surface type when utilizing breast implants for any indication.

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Legend to figures

Figure 1 : Classification of implant surfaces based on surface area/roughness[7]

Figure 2: Rise in number of diagnosed cases of BIA-ALCL in Australia & New Zealand

Figure 3: Cumulative proportion of patients with BIA-ALCL per 10,000 implants for Allergan/Inamed (biocell) versus Mentor (siltex) implants.

Table 1 Frequency of implant types associated with BIA-ALCL in this cohort of patients (n=110 implants in 81 patients due to reoperation) with comparison to previous report in 2016[3]. Grading system based on classification system published by Jones et al[7]. Mean implant duration of implant exposure prior to development of BIA-ALCL are included but these differences were not significant.

Manufacturer	Texture type	Surface area	Mean Implant duration (years)	Surface Grade[7]	No. 2016[3] n=75	No. 2018 n=110	Percentage
Allergan/ Inamed	Biocell (salt loss)	Intermediate	7.8	3	44	61	55.5
Silimed	Polyurethane	High	5.2	4	14	23	20.9
Surgitek	Polyurethane	High	25.0	4	1	1	0.9
Polytech	Polyurethane	High	4.5	4	0	1	0.9
Nagor	Nagotex (salt loss)	Low	6.4	2	5	7	6.4
Mentor	Siltex	Low	4.0	2	5	7	6.4
PIP	PIP	Low	2.3	2	2	4	3.6
Mentor	Smooth	Minimal	15.5	1	2	3	2.7
Unknown	Smooth	Minimal	15.5	1	2	2	1.8
Unknown	Textured	?	9.0	?	0	1	0.9

Table 2: TNM staging of patients in ANZ cohort with comparison to previous report[3]

Pathology	TNM	Stage	Number 2016[3]	Number 2018	Percentage	Mortality
BIA-ALCL positive in fluid but negative on capsule	T1N0M0	IA (neg)	32	51	62.9	Nil
BIA-ALCL in fluid and luminal side of capsule	T1N0M0	IA (pos)	10	13	16.0	Nil
BIA-ALCL infiltrating capsule	T3N0M0	IC	6	6	7.4	Nil
Mass extending beyond capsule	T4N0M0	IIA	5	9	11.1	2
Mass with Metastatic disease to one lymph node in axilla	T4N1M0	III	1	1	1.2	1
Mass with Metastatic disease to multiple lymph nodes	T4N2M0	III	1	1	1.2	1

Table 3 Calculated implant specific risk of BIA-ALCL per number of implants (Confidence intervals in brackets)

	Implants per ALCL
Silimed Polyurethane	2832 (1582,5673)
Biocell	3345(2475,4642)
Siltex	86029 (15440-1301759)

Figure 1

Process	Polyurethane foam	Salt Loss (Biocell/ Eurosilicone)	Gas Diffusion	Salt Loss (Nagotex)	Imprinting	Smooth/Nano
Surface Area	High	Intermediate	Intermediate	Low	Low	Minimal
Roughness	High	Intermediate	Low	Low	Low	Minimal
SURFACE TYPE	4	3	3	2	2	1

Figure 2

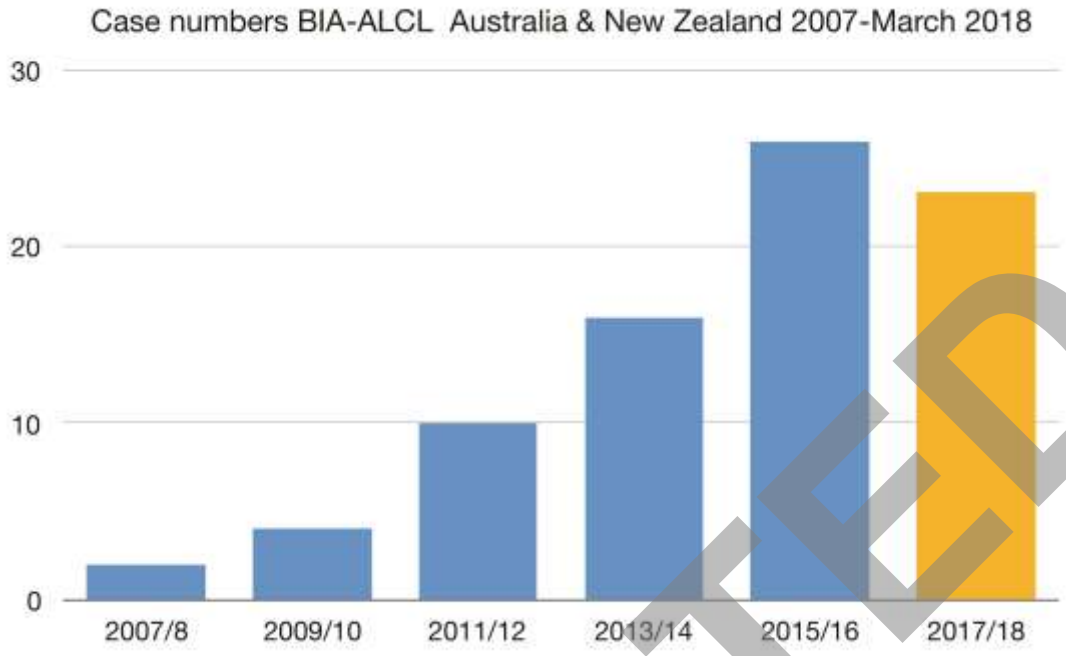

Figure 3