Breast Implant Associated Anaplastic Large Cell Lymphoma

What every plastic surgeon should know

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Kaiser Permanente
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Financial disclosures/conflicts of interest

None

Chair BIA-ALCL Taskforce for ASPS
ASPS Liaison to FDA
Coauthor Lymphoma NCCN Guidelines

ASPS ASAPS Joint Statement January 10, 2018

1. All government authorities and oncology organizations classify BIA-ALCL as a lymphoma
2. To date, only noted to occur with textured implants.
3. Report confirmed cases to ASPS/FDA PROFILE Registry
4. FDA, ASPS, ASAPS support NCCN Guidelines for Diagnosis and Treatment
5. After PET/CT for oncologic workup, Treatment is surgery with removal of implant and capsule for most patients
6. For clinical situations where use of a smooth vs. textured device is equivocal, should consider a smooth device
7. Deaths and advanced cases emphasize need for prompt identification and proper treatment


2011, 2016, 2017 FDA safety communication

• Agrees with World Health Organization BIA-ALCL is a rare T-cell lymphoma around breast implants
• Support NCCN Guidelines for diagnosis and management
• Support PROFILE Registry reporting
• 359 adverse event reports, nine deaths
• Textured surface cases predominate


2016 World Health Organization classification on lymphoma

• Worldwide consensus by pathologists, clinicians and basic scientists
• BIA-ALCL provisional classification as a lymphoma
• ALCL now has three types: ALK+, ALK-, BIA
• If confined to capsule, surgery alone

1. World Health Organization BIA-ALCL is a rare T-cell lymphoma

NCCN BIA-ALCL Guidelines 2016

• Standardized guidelines for the diagnosis and management of BIA-ALCL
• Based upon best evidence-based approach

1. NCCN Guidelines for the Diagnosis and Management of Breast Implant-Associated Anaplastic Large Cell Lymphoma

Mark Clemens, MD
2016 NCCN Guidelines

- Internationally recognised algorithms for the diagnosis and treatment of cancer
- Utilized by the majority of oncologists
- Adopted by international societies

Case study: Abby

- 70-year-old female
- 1992: mastectomy and breast reconstruction NIS implants
- 2016: acute swelling of right breast
- Ultrasound: fluid, no masses
- FNA: normal

BIA-ALCL presentation

- Effusion 79.3%
- Mass 40%
- Capsular contracture 8%
- Skin rash 2%
- Lymphadenopathy 8%

Do not test normal fluid

Images courtesy of Dr Mark Clemens.
CA/CARE Clinical Trials
Delayed seroma (>1 year)

- McGuire et al. 2017
  - 17,656 patients, 31,985 implants
  - 6 BIA-ALCL: 1.2943 (95%CI:1350-8000)
  - 9-13% of delayed seromas may be BIA-ALCL

**Case study: Abby**

- 70-year-old female
- 1992: mastectomy and breast reconstruction NS implants
- 2016: acute swelling of right breast
  - Ultrasound: fluid, no masses
  - FNA: normal

**Criteria for diagnosis of BIA-ALCL**

1. CD30+ IHC: diagnostic screen
2. Cell block cytology: large and anaplastic polymorphous cell shapes
   - Homogeneous nuclei, reniform shapes
   - Nuclear folding
3. Flow cytometry: single T-cell clone

**Case study: Beth**

- 46-year-old female
- 2016 bilateral cosmetic augmentation
- 2016: acute swelling of right breast
- FNA: ALC1

**Diagnosis of BIA-ALCL**

1. **CD30+ IHC:** diagnostic screen
2. Cell block cytology: large and anaplastic polymorphous cell shapes
   - Homogeneous nuclei, reniform shapes
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3. Flow cytometry: single T-cell clone

**Criteria for diagnosis of BIA-ALCL**

- Nucleus with large lymphoid cells and heterochromatin
- Nucleus with large lymphoid cells and pleomorphic nuclei
- Nucleus with large lymphoid cells and heterochromatin
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- Nucleus with large lymphoid cells and heterochromatin
- Nucleus with large lymphoid cells and pleomorphic nuclei
MDACC BIA-ALCL staging: Stage 1C

- T3: aggregate mass confined by the capsule
- N0, M0

13% capsule mass

Images courtesy of Dr. Mark Clemens

Mass 18-25% of BIA-ALCL
Worse Prognosis

- Important to image prior to surgery
- Must resect all of the malignancy

Images courtesy of Dr. Mark Clemens

Reported Stage Presentations Worldwide

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>MDA Solid Tumor TNM Stage</th>
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<tbody>
<tr>
<td>Brody 2015</td>
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<td>EA, EB, IC, II A, III B, IV</td>
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Preoperative Imaging Guides Surgery
Complete Resection Critical

DIEP flap recon of BIA-ALCL

Widely metastatic BIA-ALCL to bone

Surgery essential for cure

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Patients can progress or up-stage if untreated

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Event-free survival
Overall survival

Treatment after diagnosis
Limited surgery 43 52.9
Complete surgery 24 28.3
Radiation 35 40.8
Chemotherapy 51 58.4
ADT 6 6.9
Immunotherapy 2 2.3

MDACC BIA-ALCL staging: Stage 2A

- T4: invasive mass outside of capsule
- N0 M0

25% mass through capsule

Images courtesy of Dr. Mark Clemens

MDACC BIA-ALCL staging: Stage 1C

- T3: aggregate mass confined by the capsule
- N0, M0

13% capsule mass

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**Case study: Cara**

- 57-year-old female
- 1979 augmentation mastopexy
- Multiple exchanges for CC in 1999
- 2007 lymphadenopathy
  - Left capsule mass, chest wall invasion
  - Left implant removal, partial capsulectomy
  - Two cycles CHOP + left EBRT
  - Right chest wall recurrence
  - Right implant removal, total capsulectomy
  - Two cycles ESHAP + right EBRT
  - Left chest recurrent mass
  - Left EBRT boost, salvage ESHAP 5CT
  - Chest wall invasion mediastinum, pleural effusion
- 2010 death

**Understanding Beth versus Cara: Partial resection higher recurrence**

- 1995: cosmetic augmentation
- Silicone textured implants

- 2013: acute swelling of left breast
- Aspirated multiple times
- Partial capsulectomy, mastopexy, and implant removal
- Pathology: ALCL
- 2014: total capsulectomy and mass removal
- Pathology: ALCL
- No chemo or RT
- Surveillance US/CT scan every 6 months

**Retained disease on chest wall**

Posterior wall removed, found to have residual tumour – following completion capsulectomy, now disease-free 2 years, no chemo

**Case study: Dawn**

- 47-year-old female
- 2009: augmentation mammoplasty SL implants

- 2013 implant contracture, lymphadenopathy, chest wall mass
- 5/2015 implant exchange
- Dr. BIA-ALCL
- 7/2015 partial capsulectomy
- Six rounds of CHOP
- Two rounds of GDP
- Referred for hospice
- Chest wall invasion
- Mets to small bowel

**Patterns of Lymph Node Involvement**

- 13% of BIA-ALCL Cases
- 85% Axillary, 10% Supraclavular, 5% internal mammary
- Mass, LNI portend Worse Prognosis
**MDACC BIA-ALCL: Stage 4**

- T-any, N-any
- M1: distant disease spread

![Image](Image 65x94 to 288x260)

**Case study: Brentuximab**

- 47-year-old female
- 2009 augmentation mammoplasty, 5L implants
- 2015 implant contraction, lymphangiomatosis, chest wall mass
- June 2015 implant exchange
- In BIA-ALCL
- July 2015 initial presentation
- Six rounds of CHOP
- Two months of GEM
- Four months of brentuximab vedotin
- Complete response to BIA-ALCL

![Image](Image 65x313 to 288x480)

**CD30-targeted therapy**

- Adjunct chemotherapy: anthracycline based
- 100% CHOP cyclophosphamide, doxorubicin, vincristine, prednisone
- 8% ICE: ifosfamide, carboplatin, etoposide
- 4% CVAD: cyclophosphamide, vincristine, doxorubicin, dexamethasone
- BIA-ALCL: 32% recurrence rate at 3 years
- Salvage radiation therapy for unresectable disease

![Image](Image 65x532 to 288x699)

**Deaths rare,**

**Good prognosis if treated**

- 16 attributable deaths
- Delay in treatment or misdiagnosis
- 45-month mean follow up
- Range 3–217 months
- 13 years median overall survival
- 93% at 3 years
- 89% at 5 years

![Image](Image 65x243 to 288x354)

**Case Example**

- 2015 37yo female, Subglandular textured augmentation 295ml
- 5/16/2017 Periprosthetic Seroma, breast swelling
- 5/30/2017 Implant removal, seroma drainage
- 6/19/2017 Skin ulcers, antibiotics and corticosteroids, HBO₂
- 7/12/2017 Chest wall invasion, pulmonary compromise, enlargement periaortic, pre-carcinal and subcarcinal lymph nodes. Open breast capsule biopsy BIA-ALCL, CHOP initiated
- 9/28/2017 Pseudomonal infection, sepsis, respiratory failure, death

![Image](Image 324x94 to 547x260)

![Image](Image 324x532 to 547x699)
Registries Critical To Understanding

- 194 patients reported to ASIS PROFILE Registry\(^5\)
- 52 patients treated at MDACC\(^3\)

**BIA-ALCL Global Network Roundtable**

517 World Cases, Unique and pathology confirmed 16 Deaths Worldwide

- 26 countries
- Australia: 71 Cases, 3 deaths
- Belgium: 5 Cases
- Brazil: 3 Cases, 1 death
- Canada: 23 Cases
- Colombia: 6 Cases
- Denmark: 7 Cases
- Finland: 1 Case
- France: 42 Cases, 2 deaths
- Germany: 6 cases
- Israel: 5 Cases
- Mexico: 4 Cases
- Netherlands: 40 Cases, 1 Death
- New Zealand: 12 Cases, 1 death
- South Africa: 1 Case

**Comparison of Manufacturers**

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Unknown</th>
<th>Allegan/Inamed/McKernan</th>
<th>Mentor</th>
<th>Sientra/Silimed</th>
<th>Bioplasty</th>
<th>MD Anderson Tracking(^7)</th>
<th>Adapted Brody 2015(^5)</th>
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<tr>
<td>Unknown</td>
<td>22</td>
<td>86.5</td>
<td>81.2</td>
<td>71.1</td>
<td>60.4</td>
<td>64</td>
<td>57.4</td>
</tr>
<tr>
<td>Allegan/ Inamed/McKernan</td>
<td>184</td>
<td>8.7</td>
<td>33.6</td>
<td>21.6</td>
<td>10.2</td>
<td>100</td>
<td>60</td>
</tr>
<tr>
<td>Mentor</td>
<td>20</td>
<td>10.4</td>
<td>81.2</td>
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<tr>
<td>Sientra/Silimed</td>
<td>4</td>
<td>2.1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tr>
</tbody>
</table>

US MAUDE represents a nearly two manufacturer market compared with world data

**BIA-ALCL turns 20 years**

- One Year Increase: 
  - Worldwide 41%
  - US 45%
  - Deaths 77%

**Prosthesis-associated?**

- Tibial Implant
- Dental implant ALC1\(^2\)
- Chest port ALC1\(^2\)
- Total hip arthroplasties have higher rates of lymphoma\(^4\)
- Shoulder repair ALC1
- Lap Band ALC1

**Bariatric Implant–Associated Anaplastic Large-Cell Lymphoma**

- T2P
- Mucosal
- Vanishing
- T2P/Silent
- T2P/Silent/d
No Confirmed Pure Smooth Cases To Date

Out of 209 adverse event reports, 20 reports of “smooth implant” cases
Smooth implant reports had no other clinical history of a very superficial untreatable history.

70 to 80 percent of implants sold in North America are smooth.
No cases of ALCL were found in patients with documented smooth devices only.


50-year-old woman who had undergone bilateral cosmetic breast augmentation with a smooth silicone gel breast implant 19 years previously. In 2006, but device had already been replaced for the same complications.


Geographic variation?

• US: 1:30,000 (100 cases, 2016)
• Netherlands 1:6920 (32 cases)
• Australia, New Zealand, 85 cases,1,2 17 PU cases
• Risk 1:1000-1:10,000?3 for textured implants
• Allergan Biocell (1,5705)
• Sliimed polyurethane (L:3894)
• Mentor Silles (1,60631)


US incidence1

Incidence of BIA-ALCL1

1. Lifetime risk: 1:30,000 textured implants

Mechanism of Allergic Inflammation

• IL-13 is the signature cytokine of allergic inflammation
• Th2 lymphocytes and ALCL both express GATA3 (Th2 transcription factor) and both secrete IL-13
• Creates feedback loop

Determination of origin cell

• IL-13 production – allergic reaction
• IL-26 production – Th17 antibacterial cytokine
• BIA-ALCL Th17 phenotype
• Th17 contribute to pathogen clearance at mucosal surfaces and chronic inflammation
• Detailed evaluation of biomarkers
  • CD3+ in all (n=44) cases,
  • CD4+ of 62 (15%),
  • CD4+ of 6 of 37 (18%),
  • CD8+ of 4 of 5 (80%),
  • CD8+ of 4 of 5 (80%),
  • TCR-a/b 5 of 26 (22%),
  • TCR-b 5 of 26 (22%)
Finding the super antigen
- Multifactorial related to textured implant
- Silicone particulate
- Mechanical abrasion
- Bacteria/biofilm LPS

ALCL clusters on implant

Gram Negative LPS Antigen
- Ralstonia picketti
- Ralstonia spp
- Gram-Negative Bacteria

Breast Reconstruction Infection Predictors

Univariate
- BMI, p=0.04
- Age>52, p=0.05
- Comorbidity, p=0.02
- NSL, p=0.04
- High intraop fill, p=0.06

Multivariate
- NSM, p=0.06
- CA vs Proph, p=0.08
- Duct vs Lob, p=0.004
- Bra>700cc, p=0.003
- High drain time, p=0.005
- Postop XRT, p=0.02 2.3x
- SLNBx, p=0.009 2.45x
- 100cc of fill volume, p=0.001 5x

Predictors and Protectors of Infection

- Intraoperative ABX
- Betadine irrigate
- ADM use
- Drain Use duration
- Incision Placement
- Hypertension
- Duct vs Lob
- Bra>700cc
- Nipple sparing mastectomy
- Axillary Dissection
- Cosmetic versus reconstructive
- Textured Versus Smooth Implant

Macrophage Particulate Digestion
- Chronic macrophage engulfment of particulate
- Development of foamy cells
- Cytokine induced lymphocyte chemotaxis
- Synovitis rare sequelae of implant arthroplasties

Particulate digestion stimulates immune system

The Pathology of Orthopedic Implant Failure Is Mediated by Innate Immune System Cytokines

Mark Clemens, MD
Best practice: Surgery consent
Inform, not frighten

- Recommended as part of informed consent for all breast implants
- Downloadable examples
- ASPS recommendation

"The FDA has found that women with breast implants have a very low but increased risk of developing anaplastic large cell lymphoma (ALCL), a rare form of lymphoma, a cancer of the immune system. The main symptoms of ALCL in women with breast implants were a delayed fluid collection around a breast implant, often years after implant placement. Notify your health care provider if you develop any unusual signs or symptoms of your breast implants."

Report confirmed cases to PROFILE

- Patient Registry and Outcomes for breast implants and anaplastic large cell lymphoma etiology and epidemiology (PROFILE)
- Contact: ALCL@plasticsurgery.org
- ASPS/PSF FDA Cooperative Research and Development Agreement

CME: Diagnosis and Management of BIA-ALCL

- April Plastic Reconstructive Surgery Journal
- Evidence-based approach to diagnosis and management
- Mark Clemens, Garry Brody, Raman Mahabir, Roberto Miranda

Conclusions

- All implants carry a reasonable assurance of safety and efficacy
- BIA-ALCL is a lymphoma based on pathology and clinical course
- Ensure to test any late seroma more than 1 year post-implantation
- Follow NCCN guidelines for the diagnosis and management of BIA-ALCL

Do not test normal fluid!

Thank you