Breast Implant Associated – ALCL
MD Anderson Cancer Center Experience

FDA Advisory Panel
March 25, 2019

Mark W. Clemens, MD, FACS
Associate Professor
MD Anderson Cancer Center
Disclosures

Mentor Corporation: Clinical investigator for Athena Trial

Establishment Labs: Clinical investigator for US Safety/Efficacy Trial

Allergan Corporation: Former Consultant 2012-2015, Travel expenses for an educational meeting

Committee Author, National Comprehensive Cancer Network (NCCN) Lymphoma Guidelines
Comparison of Databases

<table>
<thead>
<tr>
<th>Age at time of diagnosis (yrs)</th>
<th>US Only As of 3/5/2019 (n=101)</th>
<th>All MDR Reports as of 9/30/2018 (n=660)*</th>
<th>All MDR Reports (as of 9/30/2018) (n=457)*</th>
<th>US Only As of 3/20/2019 (n=152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>55</td>
<td>53</td>
<td>53</td>
<td>54</td>
</tr>
<tr>
<td>Range</td>
<td>31-84</td>
<td>24-90</td>
<td>24-90</td>
<td>28-87</td>
</tr>
<tr>
<td>Not specified</td>
<td>n/a</td>
<td>240 (36%)</td>
<td>111 (24%)</td>
<td>n/a</td>
</tr>
<tr>
<td>Time from the last Implant to ALCL Diagnosis (yrs)**</td>
<td>Mean</td>
<td>9.1</td>
<td>9</td>
<td>8.1</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>.08-27</td>
<td>0-44</td>
<td>0-34</td>
</tr>
<tr>
<td></td>
<td>Not specified</td>
<td>4</td>
<td>231 (35%)</td>
<td>n/a</td>
</tr>
<tr>
<td>Time from Any Implant to ALCL Diagnosis (yrs)</td>
<td>Mean</td>
<td>12.7</td>
<td>n/a</td>
<td>12.6</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>2.1-44</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Not specified</td>
<td>4</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

- Short time interval to development of disease is 2.2 years from implantation
- Average time to develop disease 8-10 years
Comparison of Databases

By WHO criteria, are all CD30+ ALK –
CD30 is screening test, ALK differentiates from systemic ALCL
Comparison of Databases

<table>
<thead>
<tr>
<th>Clinical Presentation (breast)****</th>
<th>US Only As of 3/5/2019 (n=101)</th>
<th>All MDR Reports as of 9/30/2018 (n=660)*</th>
<th>All MDR Reports (as of 9/30/2018 (n=457)*</th>
<th>US Only As of 3/20/2019 (n=152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seroma</td>
<td>81</td>
<td>350</td>
<td>266</td>
<td>98</td>
</tr>
<tr>
<td>Breast swelling/pain</td>
<td>n/a</td>
<td>188</td>
<td>135</td>
<td>18</td>
</tr>
<tr>
<td>Capsular contracture</td>
<td>33</td>
<td>75</td>
<td>69</td>
<td>14</td>
</tr>
<tr>
<td>Peri-implant mass/lump</td>
<td>13</td>
<td>85</td>
<td>82</td>
<td>34</td>
</tr>
<tr>
<td>Rupture</td>
<td>n/a</td>
<td>n/a</td>
<td>54</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>n/a</td>
<td>226</td>
<td>43</td>
<td>1</td>
</tr>
<tr>
<td>Not specified</td>
<td>n/a</td>
<td>187</td>
<td>105</td>
<td>0</td>
</tr>
</tbody>
</table>

- Most common presentation delayed seroma (>1 year)
- No testing/screening of asymptomatic patients
### Comparison of Databases

<table>
<thead>
<tr>
<th>Implant Surface***</th>
<th>US Only As of 3/5/2019 (n=101)</th>
<th>All MDR Reports as of 9/30/2018 (n=660)*</th>
<th>All MDR Reports (as of 9/30/2018 (n=457)*</th>
<th>US Only As of 3/20/2019 (n=152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Textured</td>
<td>N 79 78</td>
<td>N 425 64</td>
<td>N 310 68</td>
<td>N 118 77.6</td>
</tr>
<tr>
<td>Smooth</td>
<td>N 4 4</td>
<td>N 39 6</td>
<td>N 24 5</td>
<td>N 0 0</td>
</tr>
<tr>
<td>Polyurethane</td>
<td>N/a 1 1</td>
<td>N/a n/a</td>
<td>N/a n/a</td>
<td>N/a 0.7</td>
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<tr>
<td>Not specified</td>
<td>N/a 17 17</td>
<td>N/a 196 30</td>
<td>N/a 123 27</td>
<td>N/a 33 21.7</td>
</tr>
<tr>
<td>Silicone</td>
<td>N 55 54</td>
<td>N 399 60</td>
<td>N 274 60</td>
<td>N 61 53.3</td>
</tr>
<tr>
<td>Saline</td>
<td>N 41 41</td>
<td>N 260 39</td>
<td>N 183 40</td>
<td>N 61 40.1</td>
</tr>
<tr>
<td>Implant Fill</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline/Silicone</td>
<td>N/a 1 1</td>
<td>N/a n/a</td>
<td>N/a n/a</td>
<td>N/a 0</td>
</tr>
<tr>
<td>Not specified</td>
<td>N/a 4 4</td>
<td>N/a 1 0</td>
<td>N/a 0</td>
<td>N/a 10 6.6</td>
</tr>
<tr>
<td>Reason for Implant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reconstruction</td>
<td>N 49 49</td>
<td>N 119 18</td>
<td>N 108 24</td>
<td>N 62 40.8</td>
</tr>
<tr>
<td>Augmentation</td>
<td>N 50 50</td>
<td>N 125 19</td>
<td>N 104 23</td>
<td>N 90 59.2</td>
</tr>
<tr>
<td>Not specified</td>
<td>N 1 1</td>
<td>N 416 63</td>
<td>N 245 54</td>
<td>N 0 0</td>
</tr>
<tr>
<td>Unknown</td>
<td>N 1 1</td>
<td>N/a n/a</td>
<td>N/a n/a</td>
<td>N/a n/a</td>
</tr>
</tbody>
</table>

- No only-smooth implant cases within PROFILE, MDACC, or case series
- Even mix of cosmetic/augmentation and silicone/saline
**Smooth Implant-Only Cases?**

<table>
<thead>
<tr>
<th>Implant Surface</th>
<th>Textured</th>
<th>242</th>
<th>60</th>
<th>Smooth</th>
<th>30</th>
<th>7</th>
</tr>
</thead>
</table>

4 of the 30 smooth cases had a reported history of prior implant(s), and the rest of them had not provided prior implant history.
No Confirmed Pure Smooth Cases To Date

Out of 359 adverse event reports, 28 reports of “smooth implants” cases. Smooth implant reports had either no clinical history or a very superficial unreliable 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.3


58-year-old woman who had undergone bilateral cosmetic breast augmentation with a smooth silicone gel breast implants 19 years previously. In 2006, her device had already been replaced for the same complication.2

Prosthesis-associated?

- Tibial Implant
- Dental implant ALCL\(^2\)
- Chest port ALCL\(^3\)
- Shoulder repair ALCL
- Lap Band ALCL
- Gluteal Implants x 2

Comparison of Manufacturers

Adapted Brody 2015 - World\(^2\)

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>61</td>
<td>35</td>
</tr>
<tr>
<td>Allergan/Inamed/McGhan</td>
<td>97</td>
<td>56</td>
</tr>
<tr>
<td>Mentor</td>
<td>3</td>
<td>1.7</td>
</tr>
</tbody>
</table>

**Biocell:** 8.1x Vs. All Other 32x vs. Siltex

MAUDE FDA 2017 Database\(^1,2\)

85% US, 15% OUS*

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>22</td>
<td>9.6</td>
</tr>
<tr>
<td>Allergan/Inamed/McGhan</td>
<td>184</td>
<td>80.3</td>
</tr>
</tbody>
</table>

**Biocell:** 8.3x Vs. All Other 9.2x vs. Siltex

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>68</td>
<td>44.7</td>
</tr>
<tr>
<td>Allergan/Inamed/McGhan</td>
<td>78</td>
<td>51.3</td>
</tr>
<tr>
<td>Mentor</td>
<td>6</td>
<td>3.9</td>
</tr>
</tbody>
</table>

**Biocell:** 7.1x Vs. All Other 13x vs. Siltex

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>22</td>
<td>9.6</td>
</tr>
<tr>
<td>Allergan/Inamed/McGhan</td>
<td>184</td>
<td>80.3</td>
</tr>
<tr>
<td>Mentor</td>
<td>1</td>
<td>0.6</td>
</tr>
</tbody>
</table>

**Biocell:** 8.1x Vs. All Other 32x vs. Siltex

*Unverified, unconfirmed

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CA/CARE Style 410 (Biocell) Prospective Trial

- McGuire et al. 2017
  - 17,656 patients
  - 31,985 implants
- 8 BIA-ALCL$^2$: 1:2207 (95%CI:1120,5112)

Biocell Recall

- November 21: ANSM recommends against textured implants
- December 17, 2018: CE mark withdrawal and voluntary recall for Biocell and Microcell products
- 38 countries: Europe, Israel, Brazil, Russia, Australia
- “Allergan cites an incomplete routine review and renewal of the file”
Global Risk Estimates

- US: 1:19,737 (152 cases, 2019)
  - Mixed market Allergan:Mentor
- Netherlands 1:6920 (40 cases)
  - Textured market
- Australia, New Zealand (95 cases)\(^1,2\) – Textured Market
  - Risk 1:1000-1:10,000\(^1\) for textured implants
  - Allergan Biocell (1:3345)
  - Silimed polyurethane (1:2832)
  - Mentor Siltex (1:86029)
  - 25.7 to 1 ratio of Biocell to Siltex BIA-ALCL risk

\(^1\) Therapeutic Goods Administration update, 20 December 2018; \(^2\) Magnusson M, et al. The epidemiology of breast implant–associated anaplastic large cell lymphoma in Australia and New Zealand confirms the highest risk for grade 4 surface breast implants. Plast Reconstr Surg. 2019;143:
BIA-ALCL Global Network Roundtable

427 OUS World Cases, Unique and pathology confirmed
19 Deaths Worldwide

- **35 countries**
  - Argentina: 8 cases, 1 death
  - Australia: 82 Cases, 3 deaths
  - Belgium: 10 Cases
  - Brazil: 12 Cases, 1 death
  - Canada: 25 Cases
  - Chile: 2 Cases
  - China: 0
  - Colombia: 6 Cases
  - Czech Republic: 1 case
  - Denmark: 7 Cases
  - Egypt: 1 case
  - Finland: 10 Case
  - France: 59 Cases, 4 deaths
  - Germany: 7 cases
  - Ireland: 1 case
  - Israel: 8 Cases
  - Italy: 38 Cases

- Japan: 0
- Mexico: 4 Cases
- Netherlands: 40 c, 1 Death
- New Zealand: 13 c, 1 death
- Norway: 3 cases
- Romania: 0
- Russia: 2 cases
- Singapore: 0
- South Africa: 1 Case
- South Korea: 0
- Spain: 29 Cases
- Sweden: 6 Cases, 2 death
- Switzerland: 4 cases
- Taiwan: 0
- Thailand: 1 Case
- Venezuela: 2 cases
- United Kingdom: 45 Cases, 1 death
- United States: 152 cases, 5 deaths
Published This Month – March 2019

- Supplements in ASJ and PRS journals
- 55 authors, 16 peer-reviewed articles on BIA-ALCL

- Garry Brody
- Mark W. Clemens
- Anand K. Deva
- John A. Keech
- Colleen McCarthy
- Roberto N. Miranda
- Mark Magnusson
- Arianna DiNapoli
- Dennis Hammond
- Steven Horwitz
- Meredith Collins
- L. Jeffrey Medeiros
- Daphne deJong
- Charles E. Butler
- Marshall Kadin
- Peter Lennox
- Andrea Pusic
- Gayle Gordillo
- Hinne Rakhorst
- Tony Connell
- Kelly Hunt
- Suzanne Turner
- Miles Prince
- Nadim Hallab
- Andrew Feldman
- Eric D. Jacobsen
- Greg Lamaris
- Ali Qureshi
- Ahmet Dogan
Molecular Drivers of Breast Implant-Associated Anaplastic Large Cell Lymphoma

Peter Bianco, MD
Aruna G. Naopali, MD
H. Mike Price, MD

Summary: Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is a rare neoplasm that occurs in patients with breast implants. Genetic characterization performed on BIA-ALCL to date has demonstrated qualitatively similar molecular abnormalities to those seen in its more common counterpart (ALCL-negative systemic anaplastic large cell lymphoma [SALCL]) including JAK1/STAT3 activation and MYC/TP53 dysregulation.

Theories of Etiopathogenesis of Breast Implant-Associated Anaplastic Large Cell Lymphoma

Pratik Rastogi, MBBS, GIDAAD, MS
Edward Riordan, MBBS
David Moon, MBBS
Anand K. Deva, BSc(Pharm), MBBS, MS, FRACS

Summary: Breast implant-associated anaplastic large cell lymphoma is a malignant neoplasm with rapid clinical progression. Understanding the pathogenesis of this disease is critical.

Current Risk Estimate of Breast Implant-Associated Anaplastic Large Cell Lymphoma in Textured Breast Implants

David J. Colless, MBBS
Elaine Harlton, MD
Peter Longo, FRACS
Mark Magnanoni, MBBS
Rodney Carter, MBBS, FRACS

Background: With breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) now accepted as a distinct immune system malignancy, the key to prevention is understanding the risk factors. A recent study has published a comprehensive report on the incidence and risk factors for BIA-ALCL.

Breast Reconstruction Following Breast Implant-Associated Anaplastic Large Cell Lymphoma

Gregory A. Lammaris, MD, PhD
Charles F. Butley, MD, FACS
Aruna G. Naopali, MD
H. Mike Price, MD
Robert N. Miranda, MD
Kelly K.t. Hume, MD, FRACS
Mark W. Clemens, MD, FACS

Background: Standard of care treatment of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) involves surgical resection with implant removal and complete capsulectomy. We report a case series of BIA-ALCL reconstruction with proposals for timing and technique selection.

Methods: We retrospectively reviewed and prospectively collected all BIA-ALCL patients at 2 tertiary care centers and 1 private plastic surgery practice from 1980 to 2017. Demographics, treatment, reconstruction, pathology staging, patient satisfaction, and oncologic outcomes were reviewed.

Results: We reviewed 60 consecutive BIA-ALCL patients and 18 (30%) received immediate reconstruction, and
2019 NCCN Consensus Guidelines on the Diagnosis and Treatment of Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL)

Mark W. Clemens, MD, FACS; Eric D. Jacobsen, MD; and Steven M. Horwitz, MD

The Inflammatory Effects of Breast Implant Particulate Shedding: Comparison With Orthopedic Implants

Nadim James Hallah, PhD; Lauryn Samelko, PhD; and Dennis Hammond, MD

Association Between Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) Risk and Polyurethane Breast Implants: Clinical Evidence and European Perspective

Moustapha Hamdi, MD, PhD

Genetics of Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL)

Naoki Oishi, MD, PhD; Roberto N. Miranda, MD; and Andrew L. Feldman, MD

The "Game of Implants": A Perspective on the Crisis-Prone History of Breast Implants

Anand K. Deva, BSc (Med), MBBS (Hons), MS, FRACS; Amanda Cuss, BMedSci (Hons), MBBS (Hons); Mark Magnusson, MBBS, FRACS; and Rodney Cooter, MBBS, MD, FRACS
NCCN Guidelines

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

1. Clemens MW, Jacobsen ED, Horwitz SM. Aesthet Surg J 2019
**Diagnosis BIA-ALCL**

**Symptoms**
- Effusion, mass, skin rash/ulcer
- >1 year implant
  (Average 8-10y)

**Breast Imaging**
- Ultrasound
- Or MRI

**Finding**
- Effusion
  → FNA fluid (>50ml)
- Mass
  → Incisional/core needle bx mass
  → Further imaging
- Inconclusive

**Path Workup**
- Essential for Dx
  - 1. Cytology
  - 2. Flow cytometry for T cell clone
  - 3. IHC for CD30
    Additional differentiation markers: CD2, CD3,
    CD4, CD5, CD7, CD8,

**Path Results**
- Indeterminate
- Negative for Lymphoma
  (Normal cells, Scant CD30)
- Confirmation of BIA-ALCL
  Secondary eval at tertiary cancer center
  Treat as benign seroma

**Abbreviations:** MRI Magnetic Resonance Imaging, FNA Fine needle aspiration, Bx Biopsy, CBC Complete blood count, PET/CT Positron emission tomography, CMP Complete metabolic profile, LDH Lactate dehydrogenase, RT Radiation therapy, CHOP Cyclophosphamide Doxorubicin Vincristine Prednisone, Dose adjusted Etoposide
BIA-ALCL Diagnosis

**Symptoms**
- Effusion, mass, skin rash/ulcer >1 year implant (Average 8-10y)

**Breast Imaging**
- Ultrasound
- Or MRI

**Finding**
- Effusion
- Mass
- Inconclusive
- FNA fluid (>50ml)
- Incisional/core needle bx mass
- Further imaging

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

Path Workup

- 1. Cytology
- 2. Flow cytometry for T cell clone
- 3. IHC for CD30

Additional differentiation markers: CD2, CD3, CD4, CD5, CD7, CD8, CD45, ALK

Path Results

Indeterminate

Negative for Lymphoma (Normal cells, Scant CD30)

Confirmation of BIA-ALCL
Case study: Benign Seroma Vs. BIA-ALCL


Images courtesy of Dr. Mark Clemens.
**Disease Workup**

- **Treatment BIA-ALCL**
  - **Disease Workup**
    - H&P
    - Labs: CBC with diff
    - CMP, LDH
    - Imaging: PET/CT scan
    - Recommend multidisc team
    - Oncologist lymphoma
    - Surgical oncologist
    - Plastic Surgery
    - Hemepathologist

  - **Surgery**
    - En bloc resection:
      - Total capsulectomy
      - Explantation
      - Exc mass
      - Exc biopsy node(s)
      - Consider contralateral
      - Consider delayed or immediate recon
BIA-ALCL As Two Distinct Diseases?

- Laurent 2016
- Effusion-limited (in situ) versus massively infiltrative
- Based on pathology review 19 BIA-ALCL patients to Lymphopath

*Breast implant-associated anaplastic large cell lymphoma: two distinct clinicopathological variants with different outcomes*
BIA-ALCL behaves like a SOLID tumour (like lung or breast cancer) and therefore treated surgically.¹

¹. Personal communication, Dr Mark Clemens, May 2017. Images courtesy of Dr Mark Clemens.
Treatment By Staging

**Staging**

- Disease confined to capsule (IA-IC)
  - Mass (IIA)
  - Advanced Disease (IIB-IV)

- Complete excision no residual disease
  - Incomplete excision or partial capsulectomy with residual disease

**Adjuvant Treatment**

- RT (24–36 Gy) local residual disease
- Systemic therapy:
  - Brentuximab vedotin
  - Anthracycline-based systemic ALCL regimens (CHOP, daEPOCH)

- En bloc resection
- Excision of suspicious lymph nodes
- Complete resection of capsule, including posterior wall
Complete Resection Critical

57yo 22y after cosmetic augmentation

DIEP flap recon of BIA-ALCL

BIA-ALCL Mass

DIEP Flap

Widely metastatic BIA-ALCL to bone
Staging of BIA-ALCL

US
Australia
Netherlands
Italy
# Surgery essential for cure

<table>
<thead>
<tr>
<th>Treatment after diagnosis</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited surgery</td>
<td>43</td>
<td>52.9</td>
</tr>
<tr>
<td>Complete surgery</td>
<td>74</td>
<td>85.1</td>
</tr>
<tr>
<td>Radiation</td>
<td>39</td>
<td>44.8</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>51</td>
<td>58.6</td>
</tr>
<tr>
<td>ASCT</td>
<td>6</td>
<td>6.9</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>2</td>
<td>2.3</td>
</tr>
</tbody>
</table>

## Patients can progress or up-stage if untreated

<table>
<thead>
<tr>
<th>Treatment</th>
<th>1 year (%)</th>
<th>3 years (%)</th>
<th>5 years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>35</td>
<td>50.8</td>
<td>50.8</td>
</tr>
<tr>
<td>Limited surgery</td>
<td>60</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td>Complete surgery</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Radiation</td>
<td>18</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>24</td>
<td>32</td>
<td>32</td>
</tr>
</tbody>
</table>

Total capsulectomy implant removal

- Oncologic technique¹
- Complete resection of capsule, including posterior wall
- Excision biopsy of lymph nodes

Targeted Immune Therapy - Brentuximab

- Anti-CD30 therapy\(^1\)
  - First line treatment of systemic and peripheral ALCL
  - “Preferred” in BIA-ALCL
Deaths rare, Good prognosis if treated

- 19 attributable deaths*1,2
- Delay in treatment or under-treatment
- Deaths most commonly from invasion of chest wall
Mark Clemens, MD

BIA-ALCL US Centralized Tissue Repository

Anand Deva, MacQuarie University, Australia
Marshall Kadin, Boston University, USA
Andrew Feldman, Mayo Clinic, USA
Terence Myckatyn, Wash U, USA
Suzanne Turner, Cambridge University, UK
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
Genetic Predisposition
BIA-ALCL

• JAK1/STAT3 Mutations implicated
  • Blombery 2016¹
  • Di Napoli 2016²

• Feldman 2018
• 36 cases BIA-ALCL
• All cases triple negative
  • Significant homogeneity
• 100% STAT3 Expression
• STAT3 is mediated by JAK1/STAT3 mutations

Gram Negative Biofilm Endotoxin

Shaped Versus Round

• MROC Outcomes, 11 centers
• 822 patients: Shaped vs round
• Similar PROs at two years
• 3x infection rate 6% vs. 2%, (p=0.03)
Microbiome of BIA-ALCL

- Comparison BIA-ALCL vs. Cap con vs. control
- No distinct microbiome
- Propionibacterium and Staphylococcus spp. Most common in all specimens

Effect of Anti-Infective Technique on Risk?

- Betadine breast irrigation associated with decreased capsular contracture
- Antibiotic alone may select out resistant bacteria

Intraoperative Techniques in BIA-ALCL Patients

- If operative technique could affect risk, no strategies have yet been determined

N=24 patients
- Betadine Irrigant: 12 patients (No full strength, 6 50% Strength, 4 25% Strength, 2 “tea colored”)
- Antibiotic Irrigant: 7 patients (5 Baci/Cef/Gent, 2 Polymyx/Baci)
Macrophage Particulate Digestion

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

Silicone Synovitis

*Longer Term Outcome Data and Review of the Literature*

David Pugliese, DO,* David Bush, MD,† and Thomas Harrington, MD*
Particulate digestion stimulates immune system

Activated B cells

Activated TH cells

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

Stefan Landgraeberv, Marcus Jäger, Joshua J. Jacobs, and Nadim James Hallab

1 Department of Orthopaedics, University Hospital Essen, University of Duisburg-Essen, Hufelandstrasse 55, 45122 Essen, Germany
2 Department of Orthopedics, Ruprecht University Medical Center, 60620 Marburg, Germany
Is type of texturing predictive for BIA-ALCL?
Semantics: How to Categorize Texture?

- Macro
- Aggressive
- Mid-texture
- Rough
- Micro
- Nano
- Smooth
Biocompatibility Based on Roughness

- Macrophage reaction to texturing
- Significant difference in implant hydrophobicity (P<0.0001)
- Certain surfaces promoted poor macrophage polarization (pro-inflammatory response)
- Hydrophilic less inflammatory and less bacterial adherence

# Texture Grading Classifications

## Summary of Smooth and Textured Implant Classifications

<table>
<thead>
<tr>
<th>Smooth &lt;10 μm</th>
<th>Microtextured 10 to 50 μm</th>
<th>Macrotextured over 50 μm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smooth nanotexture (80-100mm²)</td>
<td>Microtextured 100–200mm²</td>
<td>Macrotextured-Plus &gt; 300mm²</td>
</tr>
<tr>
<td>All smooth, Motiva Silk</td>
<td>All smooth, Motiva Silk and Velvet</td>
<td>Nagor, Polytech</td>
</tr>
</tbody>
</table>

### Smooth
- All smooth, Motiva silk
- All smooth

### Microtextured
- Motiva Velvet, B-Lite, Allergan Microcell/BRST, Mentor Siltex, Sientra True
- Arion Micro, Sebbin Micro, Motiva Silk/Velvet

### Macrotextured
- Allergan Biocell, Silimed PU, Polytech PU
- Allergan Microcell/Biocell, Mentor Siltex, Eurosilicone Micro, Nagor, Polytech, Silimed
- Macrotextrue-Plus > 300mm²

### Surface area
- 80-100mm²
- 100–200mm²
- 200–300mm²
- > 300mm²

### Surface area/roughness by MicroCT
- Minimal
- Low
- Intermed
- High

### Bact adhes, Surface area/roughness by profilometry
- Smooth
- Rough

### Abbreviations:
- mm² millimeters squared
- SEM scanning electron microscopy
- ISO the International Organization for Standardization
- Bact adhes bacterial adhesion

Surface area is a measure of the total area that the outer surface topography of an implant occupies and that interfaces with the patient. Surface roughness is a measure of the average height of the peaks and valleys of an implant surface.

Is ‘Macro-texturing’ predictive for ALCL?

- Surface area predictive for BIA-ALCL
- Risk may be implant specific

North America Predominantly Smooth Implants

- Smooth greater than 87% of implant market
- Trending toward smooth implants and TEs
- 3 million textured implants in US circulation
My Practice

- 2010 – 2019
- 1112 Implant Patients
- 2017 smooth implants

Implant surface by percentage of practice

- Textured Shaped
- Smooth Round

64 Cases of BIA-ALCL treated at MDACC
MD Anderson Practice

- 21 Surgeons
- ~960 Implants per year
- ~11,250 over 15 years
- Smooth implant use
MSK Single Surgeon - Cordeiro Experience

- 26+ Year practice
- 3680 patients, 5768 implants placed
- 5704 breast reconstructions
- 96% textured Biocell practice
- 8 Personal cases of BIA-ALCL (1:460)
- Now recommends smooth implants
  - Bilateral case revision, will replace both

**Best practice: Surgery consent**

**Inform, not frighten**¹

- Recommended as part of informed consent for all breast implants
- May include: CE Mark withdrawal and voluntary recall in 35 countries

“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.”¹

Retroactive Notification of Past Patients

• Example forms available from ASPS
• Memorial Sloan Kettering
• Penn State
  • 1340 patients notified, 100 patients (7.4%) asked for evaluation, 9 (0.67%) requested implant exchange
• Pat McGuire Private Practice
  • 1000 patients notified, 34 (3.4%) asked for evaluation, 1 (0.1%) elective explantation with mastopexy

Conclusions

• BIA-ALCL is a lymphoma based on pathology and clinical course

• NCCN guidelines are the standard for the diagnosis and management of BIA-ALCL

• Emerging risk stratification indicates the need for investigation of texture types

Thank you

mwclemens@mdanderson.org
@clemensmd