Gruppo di studio malattie linfoproliferative.

Rete oncologica del Piemonte e Valle d'Aosta

Torino 8 Maggio 2019

Il Linfoma Anaplastcio Correlato alle protesi mammarie

Breast-Implanted Anaplastic Large Cell Lymphoma

Umberto Vitolo

Hematology
University Hospital
Città della Salute e della Scienza
Torino, Italy

quotidianosanità.it

Scienza e Farmaci

Quotidiano on line
di informazione sanitaria
13 GENNNAIO 2019 QS

Protesi al seno della Allergan ritirate dal mercato europeo per possibile legame con una rara forma di cancro

La richiesta di sospendere la vendita arriva dall'autorità regolatoria francese (ANSM), per un possibile legame con l'insorgenza di un tumore raro, il linfoma anaplastico a grandi cellule. La decisione riguarda le protesi testurizzate, che si caratterizzano per la loro superficie ruvida e sono utilizzate soprattutto in Europa

20 DIC - L'azienda farmaceutica **Allergan** ha annunciato ieri la sospensione della vendita delle protesi al seno testurizzate e il ritiro di tutti i lotti rimanenti nei paesi dell'Unione europea. "La decisione - afferma la Reuters in una nota - deriva da una richiesta formale da parte dell'autorità regolatoria francese (ANSM - Agence Nationale de Sécurité du Médicament et des Produits de Santé) sulle protesi della multinazionale, che sono state collegate a una rara forma di cancro".

"Mentre la Allergan rimarcava la sicurezza delle proprie protesi, il valore delle sue azioni in borsa calava del 7,4% a seguito delle preoccupazioni di alcuni analisti di Wall Street sulla tenuta dell'azienda rispetto alla possibilità futura di dover rispondere per danni da prodotti difettosi.

Il 18 dicembre, l'agenzia regolatoria francese aveva annunciato la richiesta di ritiro delle protesi testurizzate della Allergan a causa del mancato rinnovo delle certificazioni di sicurezza da parte di un'altra agenzia.

Le protesi al seno testurizzate, caratterizzate da una superficie ruvida e utilizzate soprattutto in Europa, sono state collegate a una rara forma di cancro, il linfoma anaplastico a grandi cellule.

Comunicato Ministero della Salute
21 Dicembre 2018

Ministero della Salute

Protesi mammarie ed espansori tissutali della ditta Allergan Limited, scadenza del certificato CE

Ad oggi non sussiste alcun incremento del rischio e non vi è alcuna indicazione al richiamo dei pazienti già impiantati. Nessun ulteriore controllo clinico di follow-up deve essere eseguito in aggiunta a quanto regolarmente già prescritto dal proprio medico curante. E' quanto sottolinea il Ministero in merito alla scadenza, il 16 dicembre 2018, del certificato CE per le protesi mammarie a superficie testurizzata (Microcell e Biocell) ed espansori tissutali della ditta **Allergan Limited**.

L'Organismo Notificato francese GMED ha richiesto, infatti, alla ditta, in data 14 dicembre 2018, documentazione aggiuntiva prima di procedere al rinnovo del certificato CE. La ditta Allergan Limited sta collaborando con l'Organismo Notificato al fine di fornire quanto richiesto. Nel frattempo la ditta Allergan Limited ha **sospeso la fornitura** dei dispositivi coperti dal certificato CE scaduto e procederà ad un ritiro dal mercato delle scorte rimanenti degli stessi.

Le Protesi Mammarie, comunemente impiantate per ragioni estetiche o ricostruttive, sono dei dispositivi medici ed in quanto tali regolamentate dal D.L 24 febbraio 1997, n. 46, attuazione della Direttiva Europea 93/42/EEC. In quanto dispositivi invasivi, perché destinate a penetrare nel corpo ed a lungo termine, vengono inquadrate come dispositivi medici di classe III. Esse appartengono, pertanto, alla classe di rischio più alta per la quale è previsto che l'Organismo Notificato, prima di rilasciare la certificazione CE, e quindi prima della immissione sul mercato, valuti con particolare attenzione la progettazione, qualità e produzione.

Il certificato CE di ogni dispositivo medico ha una validità limitata nel tempo. In prossimità della data di scadenza, e prima di procedere al rinnovo dello stesso certificato, è compito dell'Organismo Notificato procedere ad una nuova verifica e valutazione del dispositivo.

Presentation Outline

- ✓ Epidemiology and correlation with implants
- ✓ Pathogenetic hypothesis
- ✓ Clinical Presentation
- ✓ Evaluation exams and diagnosis
- ✓ Staging
- ✓ Treatment

Breast Lymphomas

Breast Lymphomas

- 90% B cell: If localized = DLBCL, Burkitts, MZL
- 10% T cell
  - PTCL (NOS)
  - ALCL
    - Systemic – ALCL Alk pos
    - Systemic – ALCL Alk neg
    - Primary Cutaneous ALCL [Alk neg]
    - Implant associated ALCL [Alk neg]

Better recognition?
Better reporting
True increase

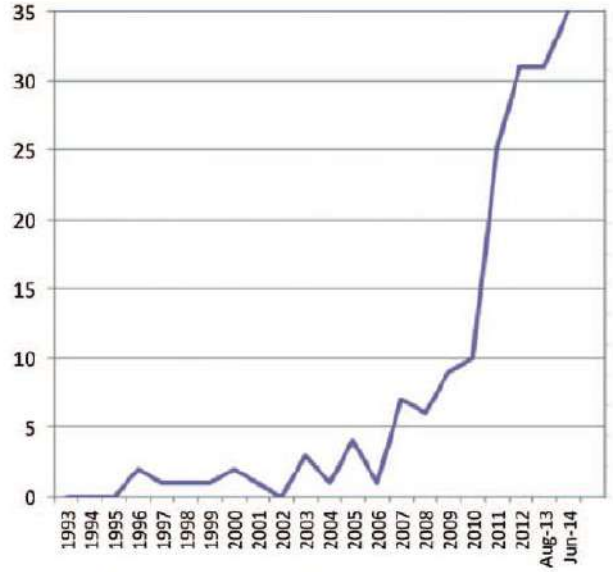


Fig. 3. Number of newly diagnosed patients per year (where date is known) through June 1, 2014.

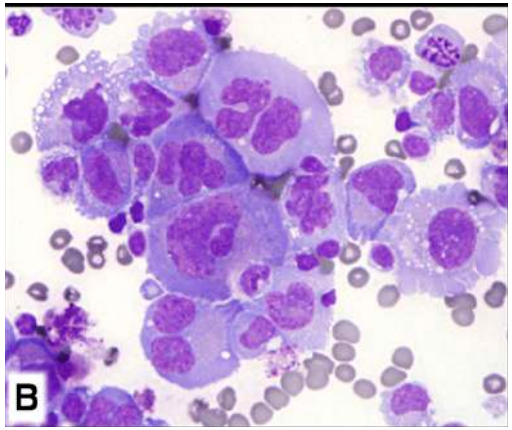
Brody et al. Plast Glob Open 2015; 3e296

The 2016 revision of the World Health Organization classification of lymphoid neoplasms

Steven H. Swerdlow,[1] Elias Campo,[2] Stefano A. Pileri,[3] Nancy Lee Harris,[4] Harald Stein,[5] Reiner Siebert,[6] Ranjana Advani,[7] Michele Ghielmini,[8] Gilles A. Salles,[9] Andrew D. Zelenetz,[10] and Elaine S. Jaffe[11]

Table 2. (continued)

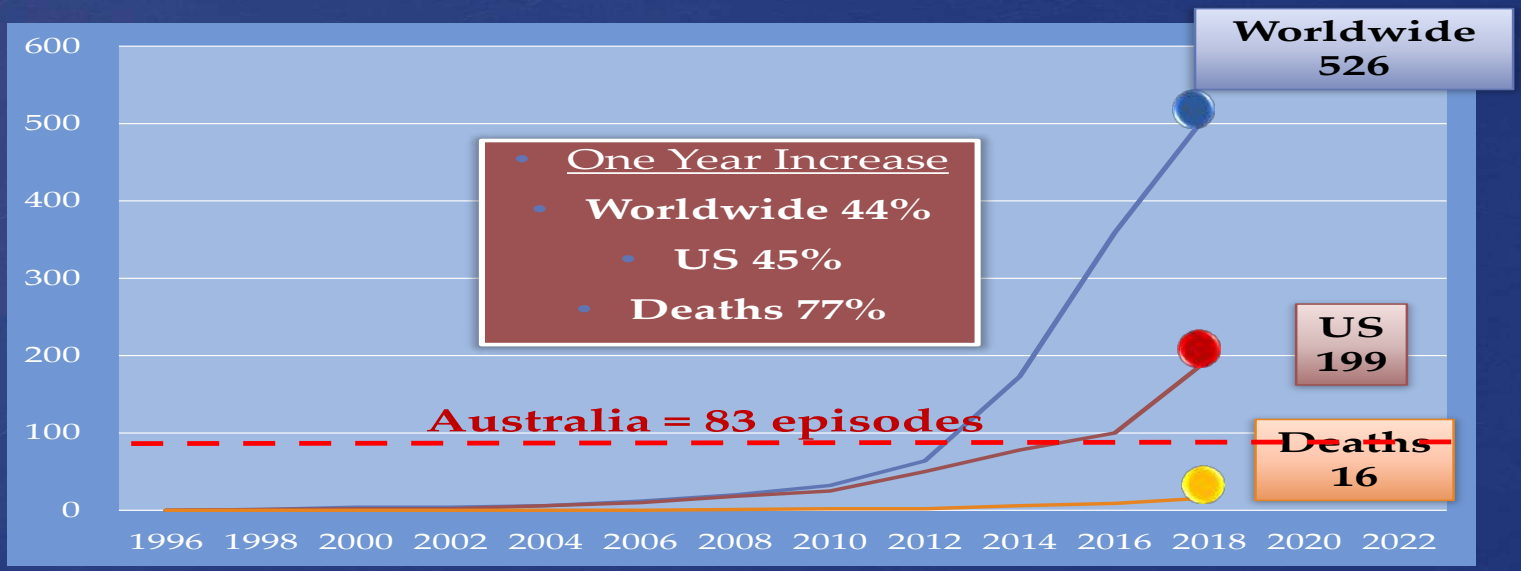
Entity/category	Change
Primary cutaneous CD4$^+$ small/medium T-cell lymphoproliferative disorder	• No longer to be diagnosed as an overt lymphoma due to limited clinical risk, localized disease, and similarity to clonal drug reactions. • Remains a provisional entity.
Peripheral T-cell lymphoma (PTCL), NOS	• Subsets based on phenotype and molecular abnormalities being recognized that may have clinical implications but are mostly not a part of routine practice at this time.
Nodal T-cell lymphomas with T-follicular helper (TFH) phenotype	• An umbrella category created to highlight the spectrum of nodal lymphomas with a TFH phenotype including angioimmunoblastic T-cell lymphoma, follicular T-cell lymphoma, and other nodal PTCL with a TFH phenotype (specific diagnoses to be used due to clinicopathologic differences). • Overlapping recurrent molecular/cytogenetic abnormalities recognized that potentially could impact therapy.
ALK$^-$ anaplastic large-cell lymphoma	• Now a definite entity that includes cytogenetic subsets that appear to have prognostic implications (eg, 6p25 rearrangments at *IRF4/DUSP22* locus).
Breast implant–associated anaplastic large cell lymphoma	• New provisional entity distinguished from other ALK$^-$ ALCL; noninvasive disease associated with excellent outcome.
Nodular lymphocyte–predominant Hodgkin lymphoma	• Variant growth patterns, if present, should be noted in diagnostic report, due to their clinicopathologic associations. • Cases associated with synchronous or subsequent sites that are indistinguishable from T-cell histiocyte-rich large B-cell lymphoma (THRLBCL) without a nodular component should be designated THRLBCL-like transformation.
Lymphocyte-rich classical Hodgkin lymphoma	• Features recognized that are intermediate between NLPHL and other types of classical Hodgkin lymphoma.
Erdheim-Chester disease	• Should be distinguished from other members of the juvenile xanthogranuloma family; often associated with *BRAF* mutations.
Other histiocytic/dendritic neoplasms	• Clonal relationship to lymphoid neoplasms recognized in some cases.



A number of studies in recent years have identified a unique form of ALK2 ALCL arising in association with breast implants designated as **breast implant–associated ALCL (Figure 6B).** First described in 1997, it usually presents as an accumulation of seroma fluid between the implant itself and the surrounding fibrous capsule.

Swerdlow SH et al Blood 2016

BIA-ALCL at 21 years



All unique cases from 28 countries. US data from PROFILE Registry, www.thepsf.orf/PROFILE

Epidemiology

- **USA: 550,000 implants/year; lifetime risk 1: 30.000**
- **Dutch Registry: 1: 6920**
- **Italian Registry: 22 cases at 2017; 2.8:100.000 patients**
- **Other countries: lifetime risk 1:1000-1:10.000**

BIA-ALCL: geographic variation?

- US: 1:30,000 (100 cases, 2016)
- Netherlands 1:6920 (32 cases)
- Australia, New Zealand, 83 cases,[1,2]
  17 PU cases
  - Risk 1:1000-1:10,000?[1] for textured implants
  - Allergan Biocell (1:3705)
  - Silimed polyurethane (1:3894)
  - Mentor Siltex (1:60631)


U.S. Epidemiology of Breast Implant–Associated Anaplastic Large Cell Lymphoma


13:46 BREAST-IMPLANT ASSOCIATED ANAPLASTIC LARGE CELL LYMPHOMA (BIA-ALCL): RELATIVE AND ABSOLUTE RISK ASSESSMENT BASED ON 100% OF ALL NATIONAL CASES OF BIA-ALCL IN THE NETHERLANDS

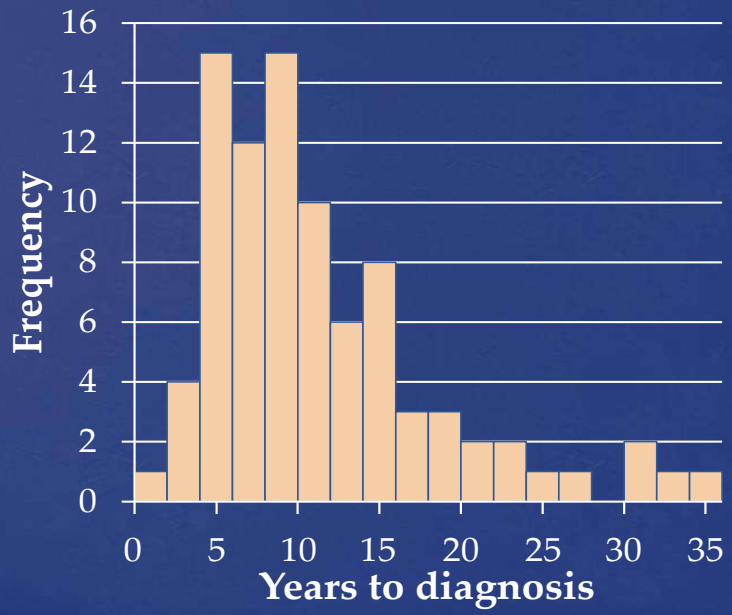
Mintsje DE BOER, René DAN DER HULST, Floor VAN LEEUWEN, Daphne DE JONG, Hinne RAKHORST
Maastricht University Medical Centre, Maastricht, The Netherlands

- Variables that may be important?
  - Usually 4 years + post implant – will it increase?
  - Geography - suggests a region/ethnic/HLA? - effect
    - 1 asians only reported (Thailand)
    - 1 Native American
    - few African American
    - Relatively few in Sth America
    - Australia/NZ over-represented

By Courtesy of Prince HN, PMcCC Melbourne

BIA-ALCL: correlation with implants

Implants

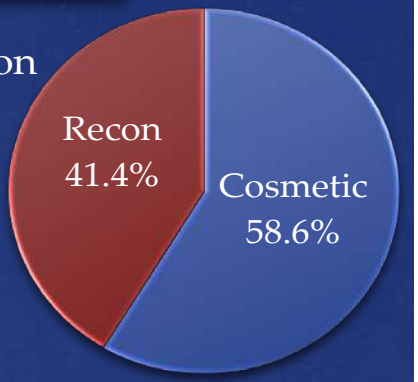


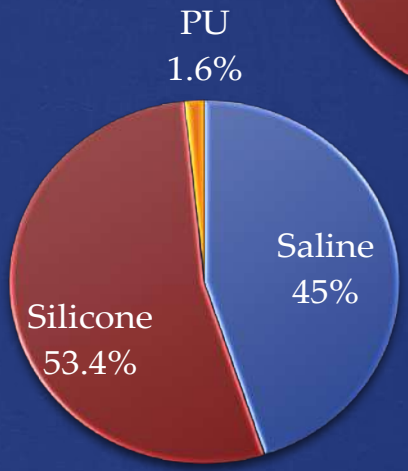
Median onset ALCL from implantation:
8 years (range, 2– 25 years)

Personal communication, Dr Mark Clemens, July 2015.

Implant Characteristics

Implant Indication





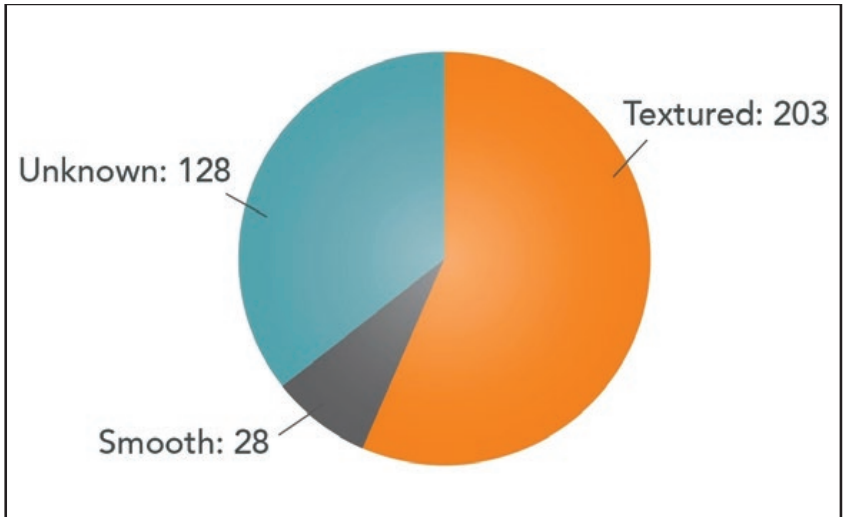
Shell Type

By Courtesy of Prince HN, PMcCC Melbourne

BIA-ALCL: correlation with type of implants

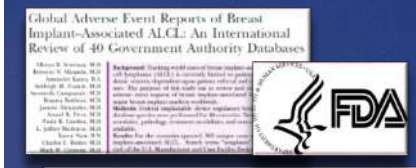
Type of implant varies from country to country

- US mostly smooth (70-80%)
- Europe and Australia mostly textured (70-90%)



BIA-ALCL reports grouped by implant surface (numbers provided in February 21, 2017 FDA update) (based on cases reported to the MAUDE Database).

No Confirmed Pure Smooth Cases To Date


Global Adverse Event Reports of Breast Implant-Associated ALCL: An International Review of 40 Government Authority Databases

FDA

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.


SPECIAL TOPIC

Anaplastic Large Cell Lymphoma Occurring in Women with Breast Implants: Analysis of 173 Cases

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]


Risk of lymphoma in women with breast implants: analysis of clinical studies

Joan Largent[a], Michael Oefelein[b], Hilton M. Kaplan[a], Ted Okerson[a] and Peter Boyle[b]

Age 71: left breast cancer (1980), treated with radiotherapy and reconstructive breast surgery (device unknown). Right breast cancer (1990) treated with mastectomy and reconstructive surgery (device unknown).[1]


ALK-1–Negative Anaplastic Large Cell Lymphoma Associated With Breast Implants: A New Clinical Entity

Abstract

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]

1. Largent J, et al. Eur J Cancer Prev 2012, 21:274–280; Lazzeri D, et al. Clin Breast Cancer 2011;11(5):283–96; 3. Brody GS, et al. Plast Reconstr Surg 2015; 135:695–705.

By Courtesy of Prince HN, PMcCC Melbourne
Calobrace MB et al, Aesthet Surg J 2017

FEBBRAIO 7, 2019

FDA: All Healthcare Providers Should Be Aware of Breast Implant Associated-Anaplastic Large Cell Lymphoma

While the majority of patients who develop BIA-ALCL have had textured implants, and most cases reported in the literature describe individuals who have had textured implants, there have been reports of BIA-ALCL in patients with smooth-surfaced implants and many reports do not include the surface texture of the implant at the time of diagnosis.

The FDA's additional data analysis identified 457 unique MDRs for BIA-ALCL, including the death of 9 patients which may be attributable to BIA-ALCL. However, it is important to note that at the time of diagnosis, patients may have their original breast implants or they may have had 1 or more replacements.

Though the number of identified cases of BIA-ALCL is small compared with the estimated 1.5 million patients who receive breast implants worldwide every year, confirmed data and published information reviewed to date suggests that patients with breast implants have an increased risk of BIA-ALCL.

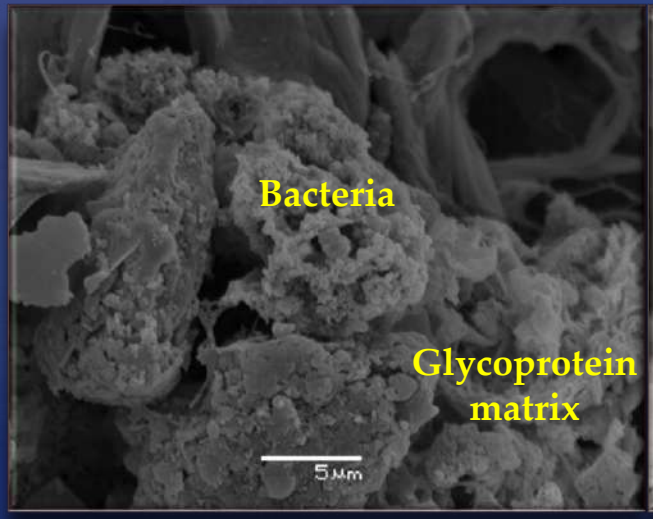
Prior to implantation, provide all patients with the breast implant manufacturer's labelling, including the patient-specific labelling, as well as other educational material prior, and make sure they are aware of the benefits and risks of the different types of implants. Most confirmed cases of BIA-ALCL have occurred in patients with textured surface implants, although there are known cases in patients with only smooth-surface breast implants.

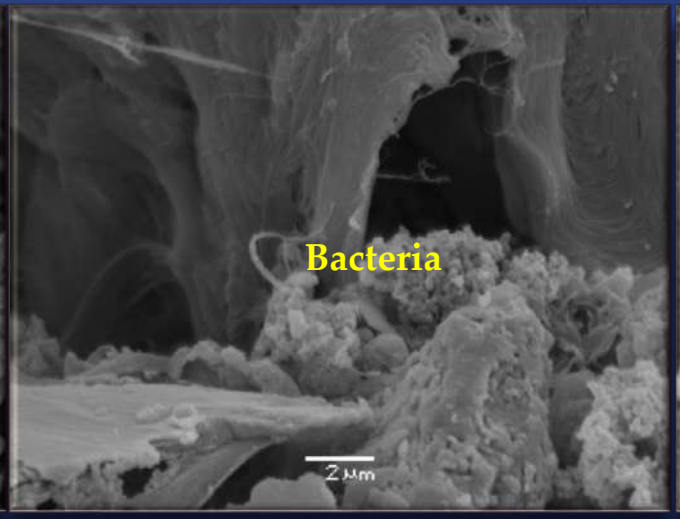
Presentation Outline

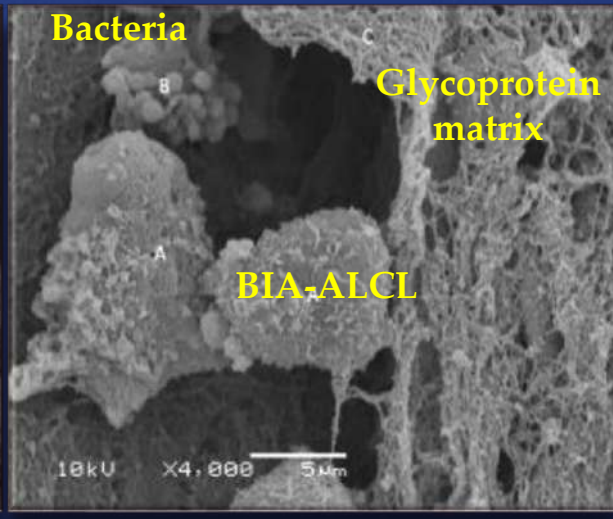
- ✓ Epidemiology and correlation with implants
- ✓ Pathogenetic hypothesis
- ✓ Clinical Presentation
- ✓ Evaluation exams and diagnosis
- ✓ Staging
- ✓ Treatment

Biofilm Theory

- Picketti Ralstonia[1]: Common in BIA-ALCL
- Precedence: Helicobacter pylori and GALT[1]
- Distinct Microbiome may chronically stimulate T-cells







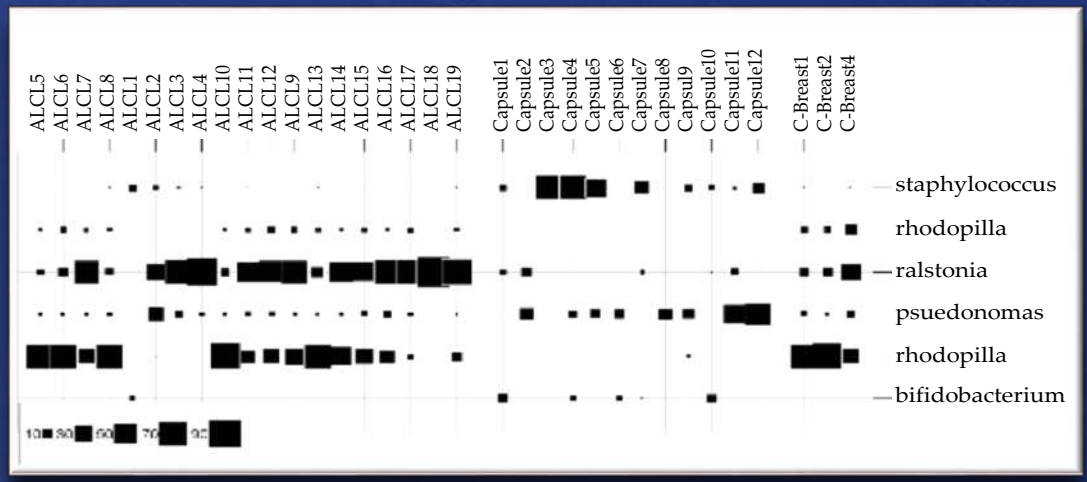
Images courtesy of Dr Mark Clemens.

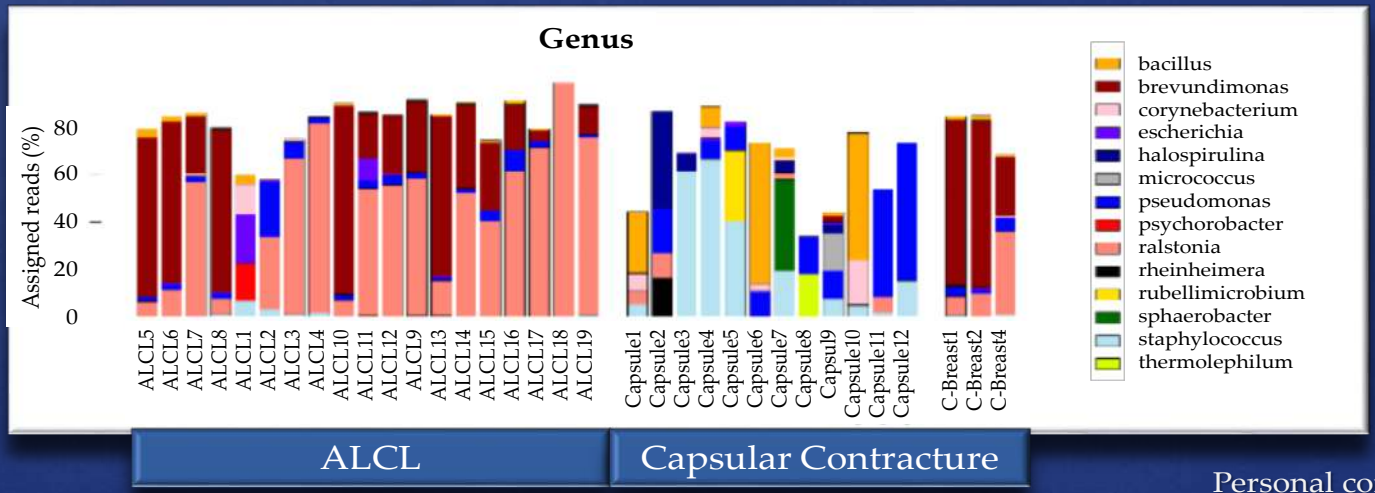
GALT = gut-associated lymphoid tissue.

1. Hu H, et al. Plast Reconstr Surg 2015;135(2):319–29; 2. Personal communication, Dr Mark Clemens, July 2015.

Biofilm

- 26 Samples analyzed for biofilm
  - Locations: USC, MDA, PMC, WM, IPS
  - SEM, PCR, FISH
- Compared to 62 capsular contracture specimens
- Distinct microbiome

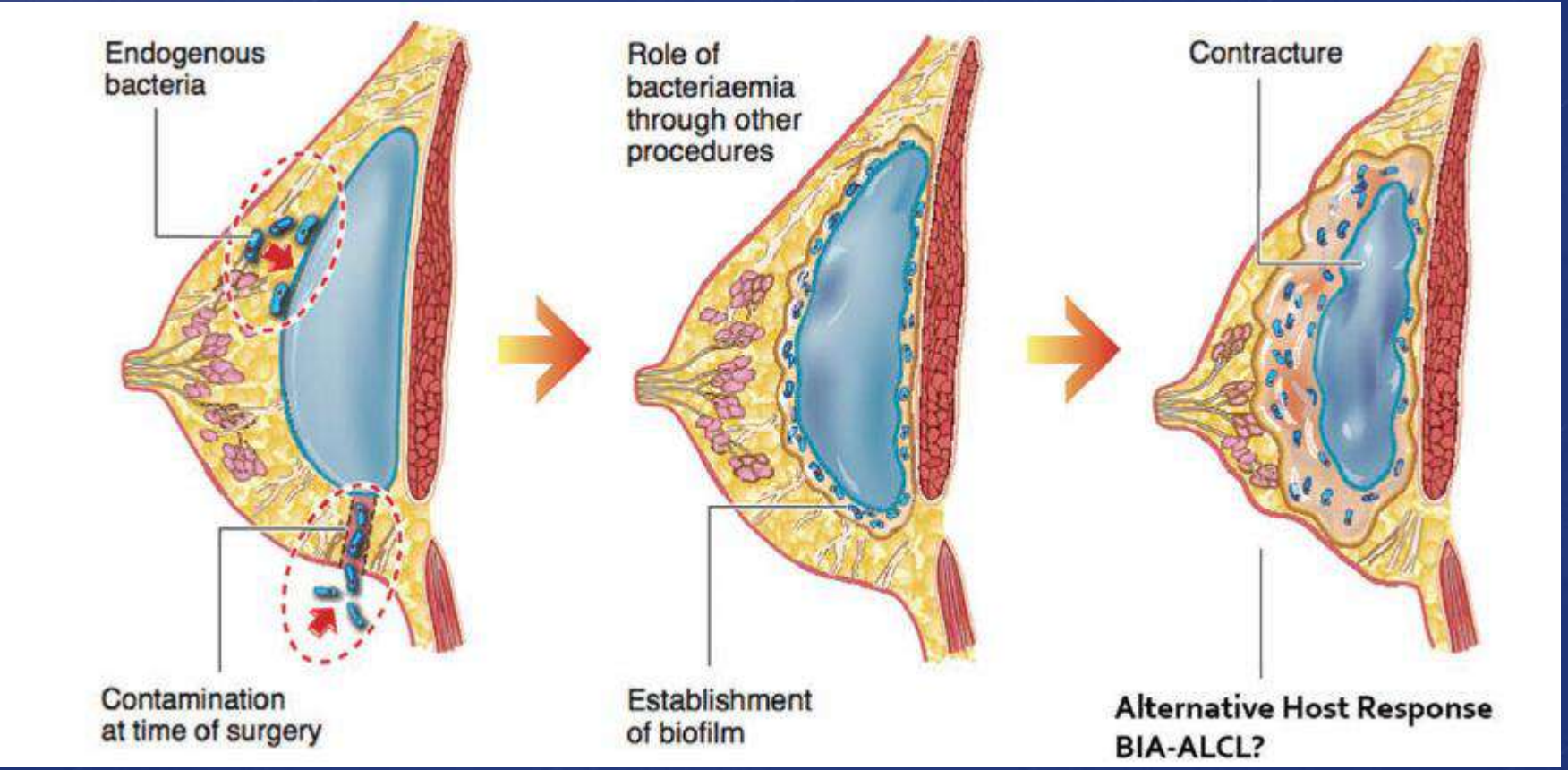




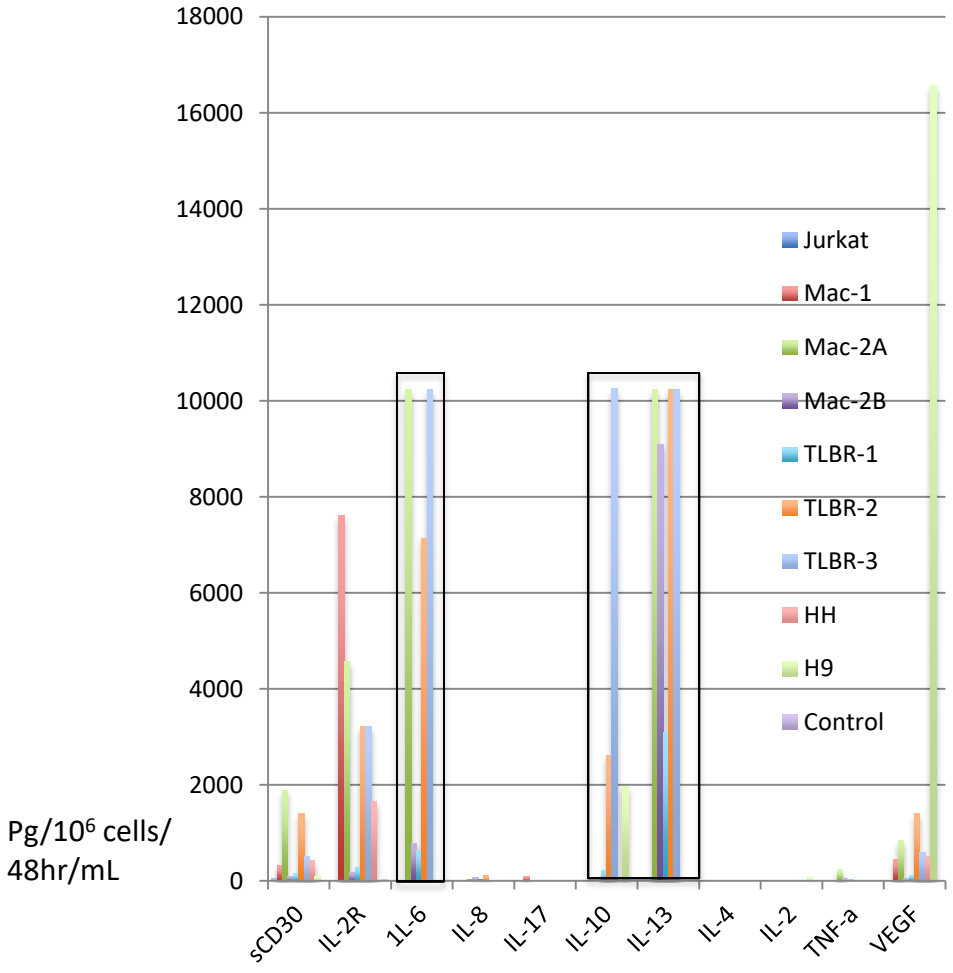
Personal communication,
Dr Mark Clemens, July 2015.

By Courtesy of Prince HN, PMcCC Melbourne

Biofilm causes a microbiome:
results in contracture and BIA-ALCL
.....but due to different host response.

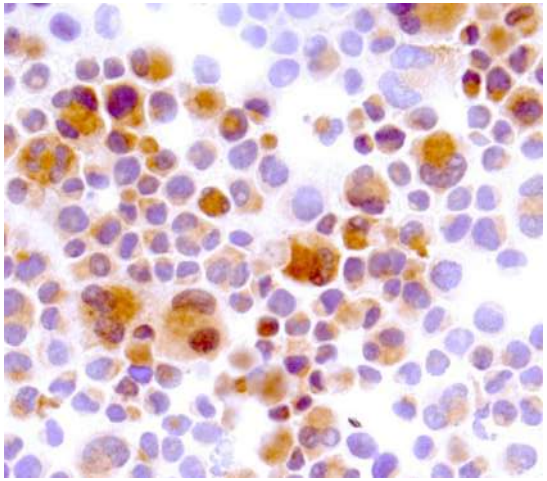


Cytokines secreted by cutaneous and BIA-ALCL lines

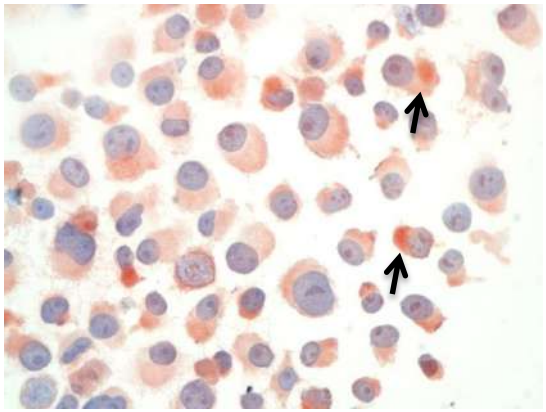


TLBR3

IL-13

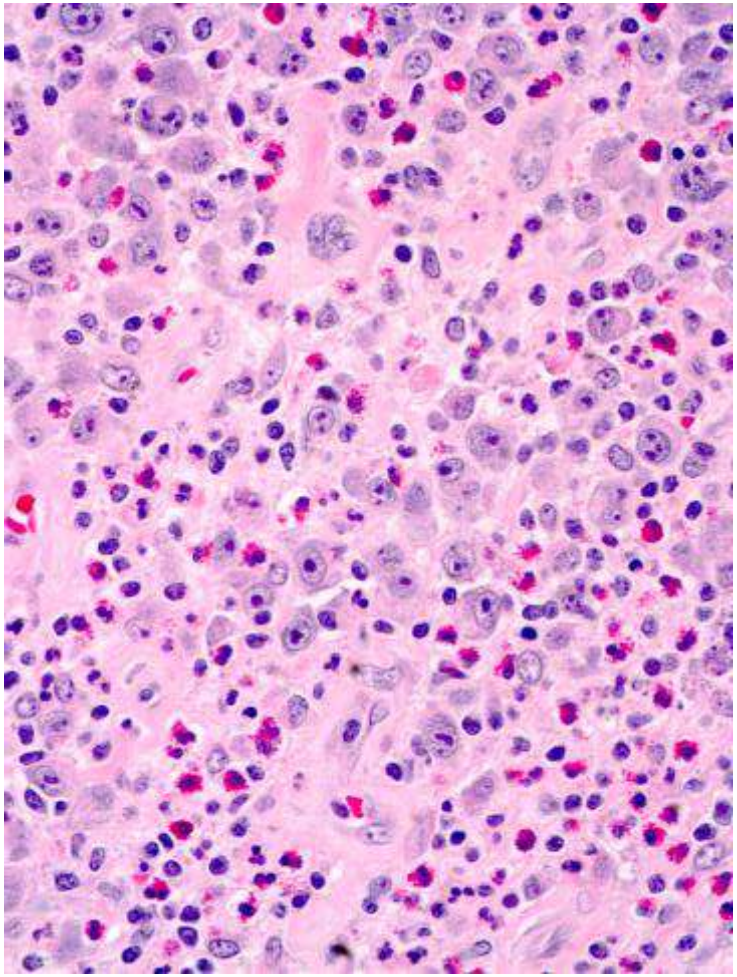


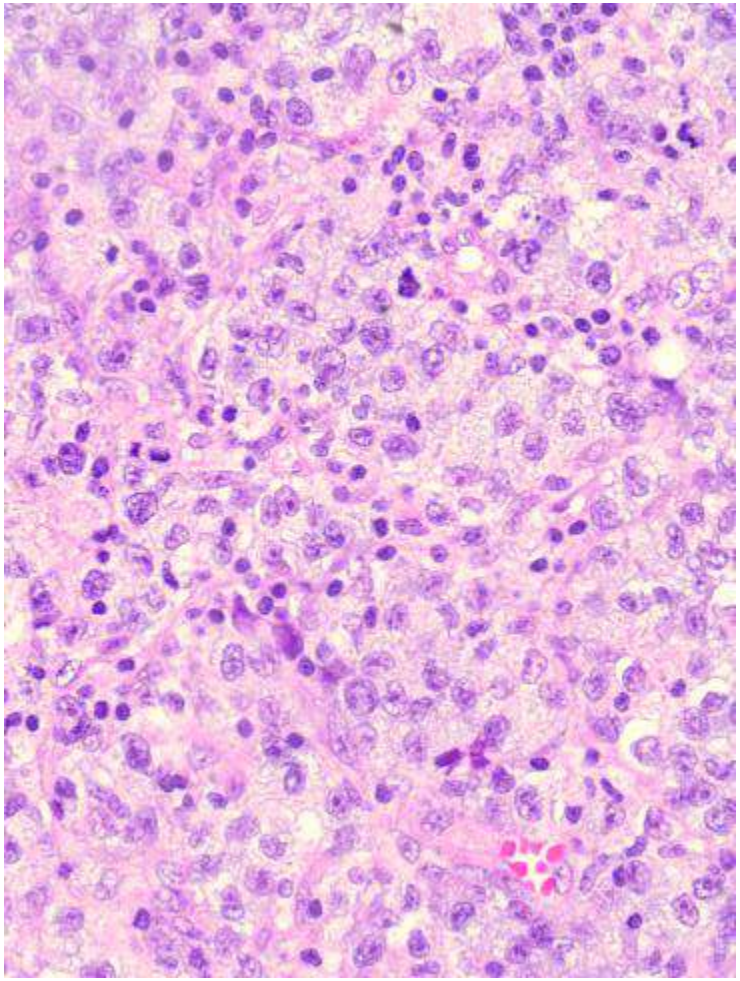
IL-10



Courtesy of Marshall Kadin, MD

Eosinophils are characteristic of BIA-ALCL but not systemic ALCL

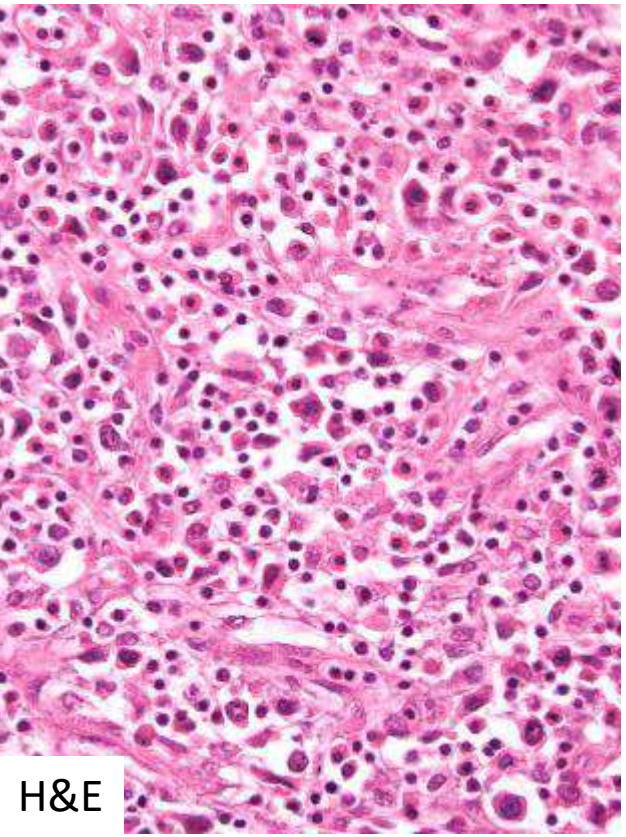




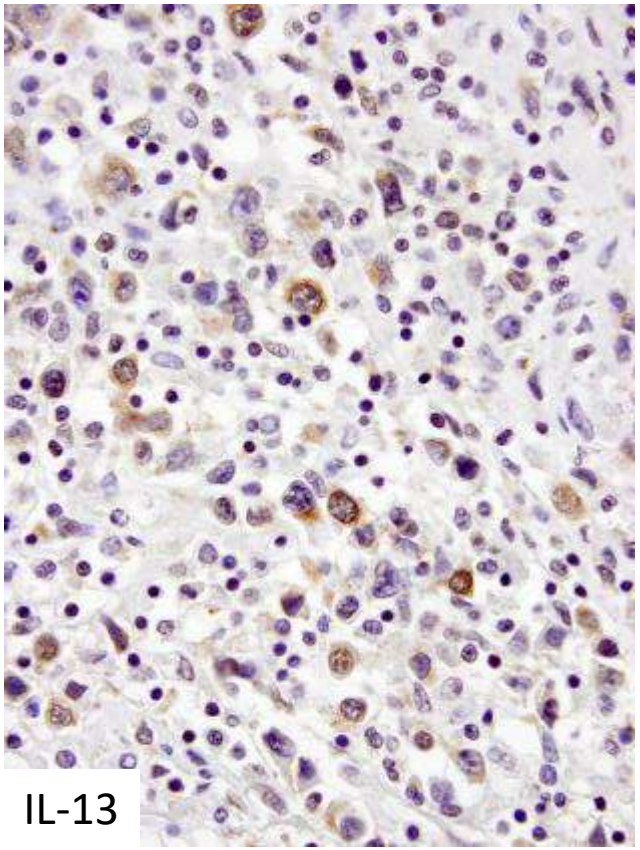
Difference in eosinophils between BIA- and systemic ALCL, P=.003, Kruskall-Wallis

Courtesy of Marshall Kadin, MD

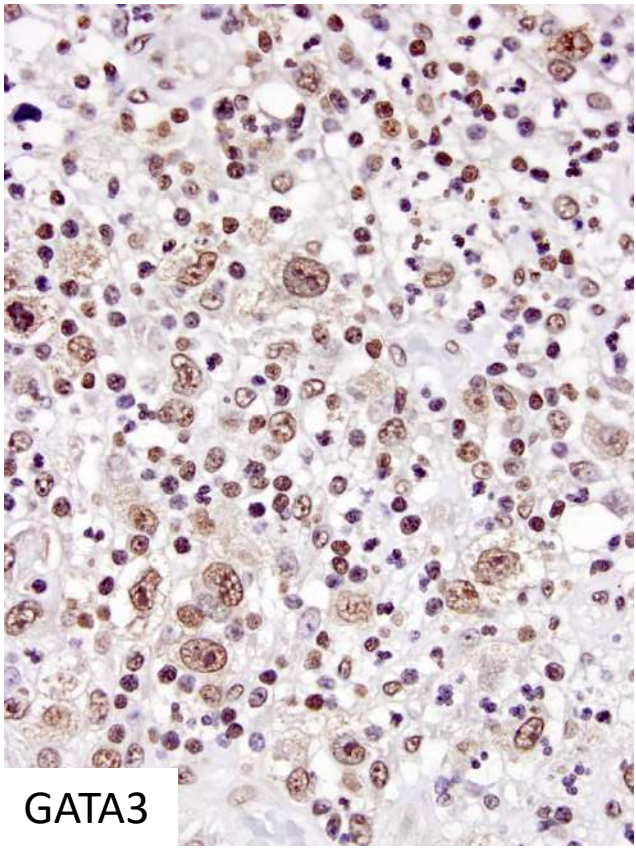
Anaplastic cells surrounded by eosinophils produce IL-13



H&E



IL-13

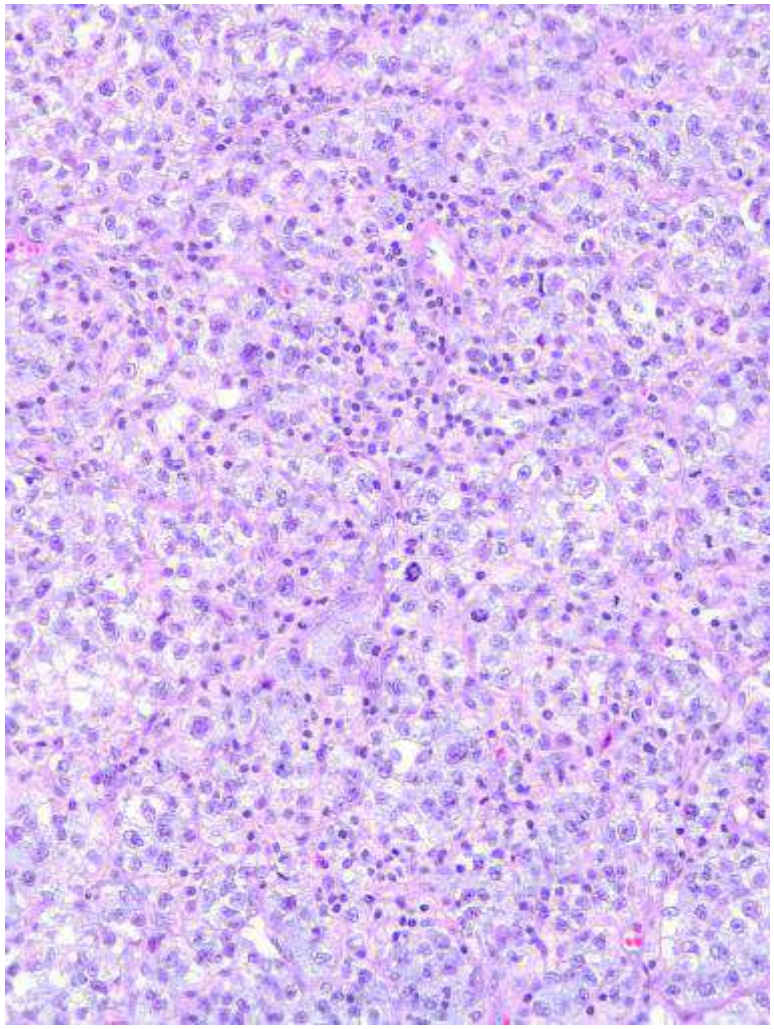


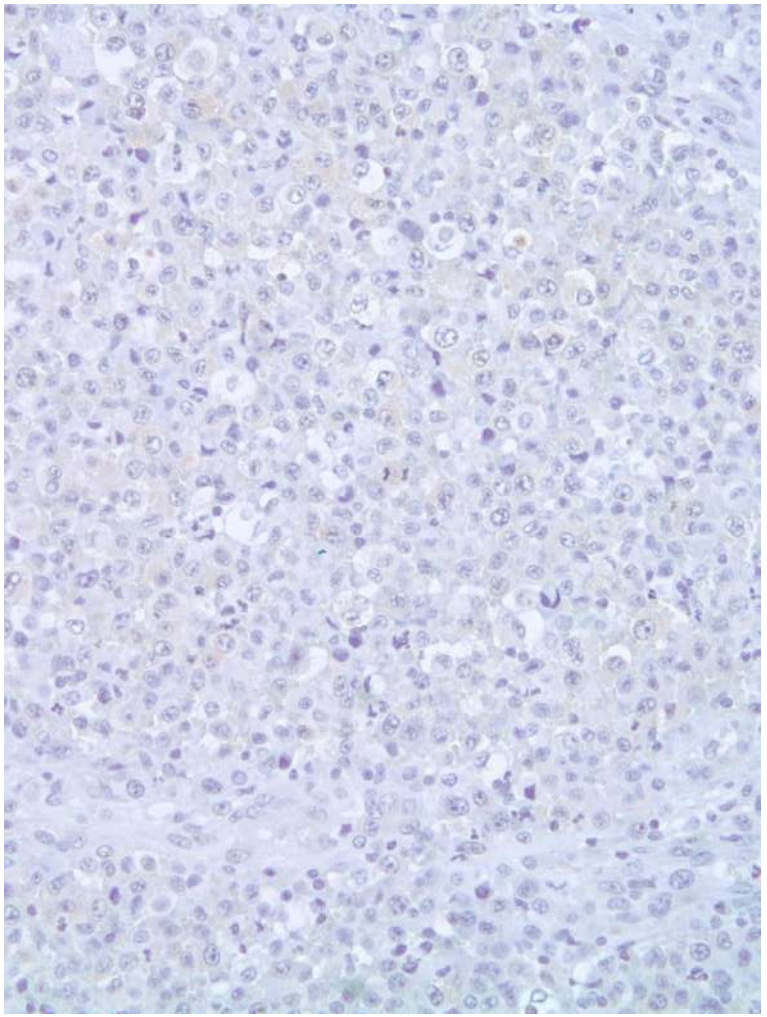
GATA3

Tumor cells surrounded by eosinophils

Courtesy of Marshall Kadin, MD

Systemic ALCL negative for IL-13





Only 2 of 18 systemic ALCL contained neoplastic cells expressing IL-13 (P< .001)

Courtesy of Marshall Kadin, MD

EUROPEAN HEMATOLOGY ASSOCIATION

haematologica

Journal of the European Hematology Association

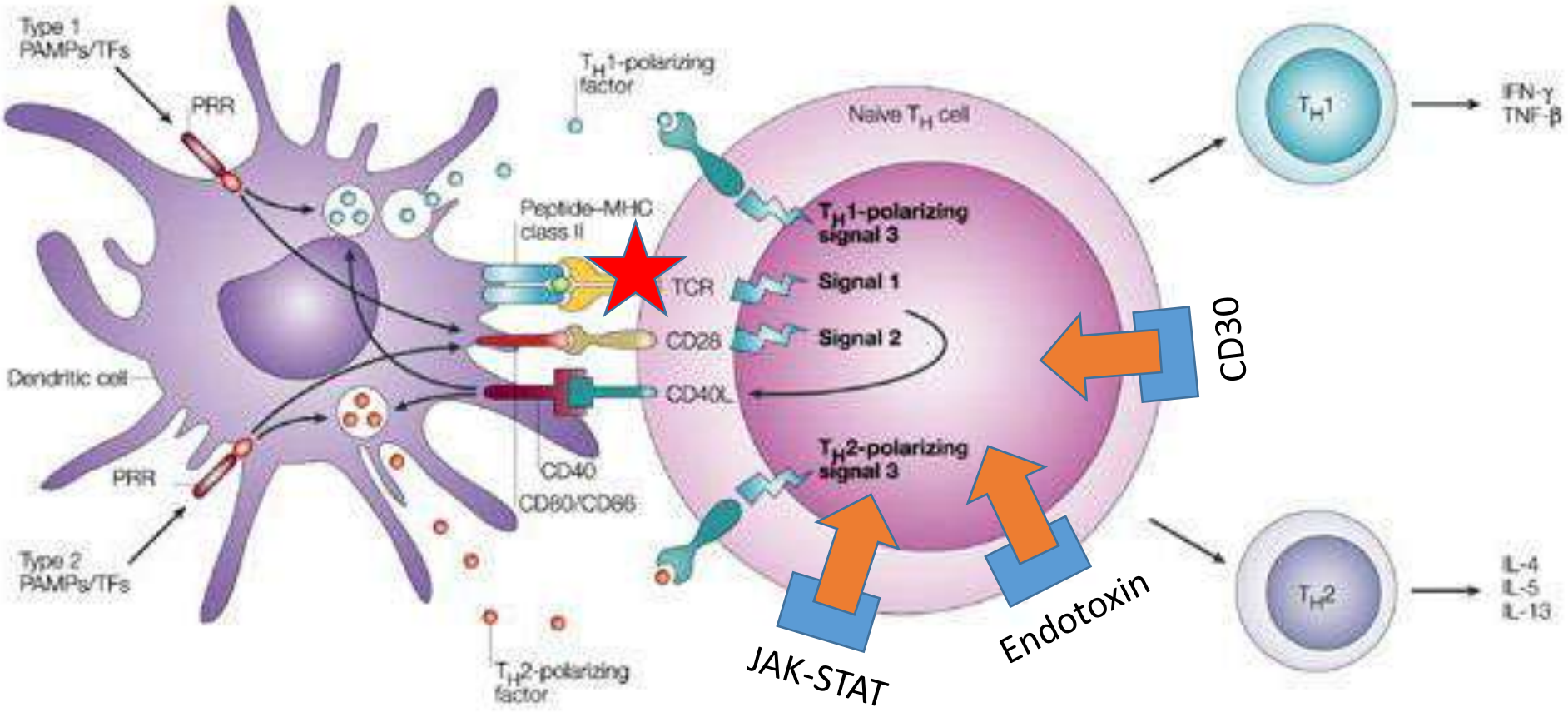
Whole exome sequencing reveals activating JAK1 and STAT3 mutations in breast-implant associated anaplastic large cell lymphoma

by Piers Blombery, Ella Thompson, Kate Jones, Gisela Mir Arnau, Stephen Lade, John F. Markham, Jason Li, Anand Deva, Ricky W. Johnstone, Amit Khot, H. Miles Prince, and David Westerman

Summary of mutations found in 10 cases from PMCC

BALCL1	*STAT3* ★	NM_139276.2:c.1981G>T; p.(Asp661Tyr)	
BALCL1	*BCOR*	NM_017745.5:c.4424G>A; p.(Trp1475*)	(bcl-6 path)
BALCL2	*STAT3* ★	NM_139276.2:c.1919A>T; p.(Tyr640Phe)	
BALCL3	*TP53*	NM_000546.5:c.673-1G>A	Confirmed germline
BALCL3	*OBSCN*	NM_052843.3:c.19411G>A; p.(Asp6471Asn)	calmodulin
BALCL4	*SOCS1* ★	NM_003745.1:c.518dup; p.(Leu174Alafs*79)	
BALCL5	*STAT3* ★	NM_139276.2:c.1981G>T; p.(Asp661Tyr)	
BALCL5	*BRIP1*	NM_032043.2:c.487C>G; p.(Pro163Ala)	With BRCA-1
BALCL6	*TP53*	NM_000546.5:c.524G>A; p.(Arg175His)	
BALCL6	*STAT3* ★	NM_139276.2:c.1229A>G; p.(His410Arg)	
BALCL6	*TP53*	NM_000546.5:c.746G>A; p.(Arg249Lys)	Confirmed germline
BALCL6	*SETD2*	NM_014159.6:c.2893G>T; p.(Glu965*)	HMT
BALCL7	*STAT3* ★	NM_139276.2:c.1840A>C, p.(Ser614Arg)	
BALCL8	*JAK1* ★	NM_002227.2:c.3290_3291delinsTT; p.(G1097V)	
BALCL8	*JAK3*	NM_000215.3:c.2164G>A, p.(Val722Ile)	Confirmed germline
BALCL9	*STAT3* ★	NM_139276.2:c.1981G>T; p.(Asp661Tyr)	
BALCL10	*STAT3* ★	NM_139276.2:c.1842C>A; p.(Ser614Arg)	

Proliferation to malignancy



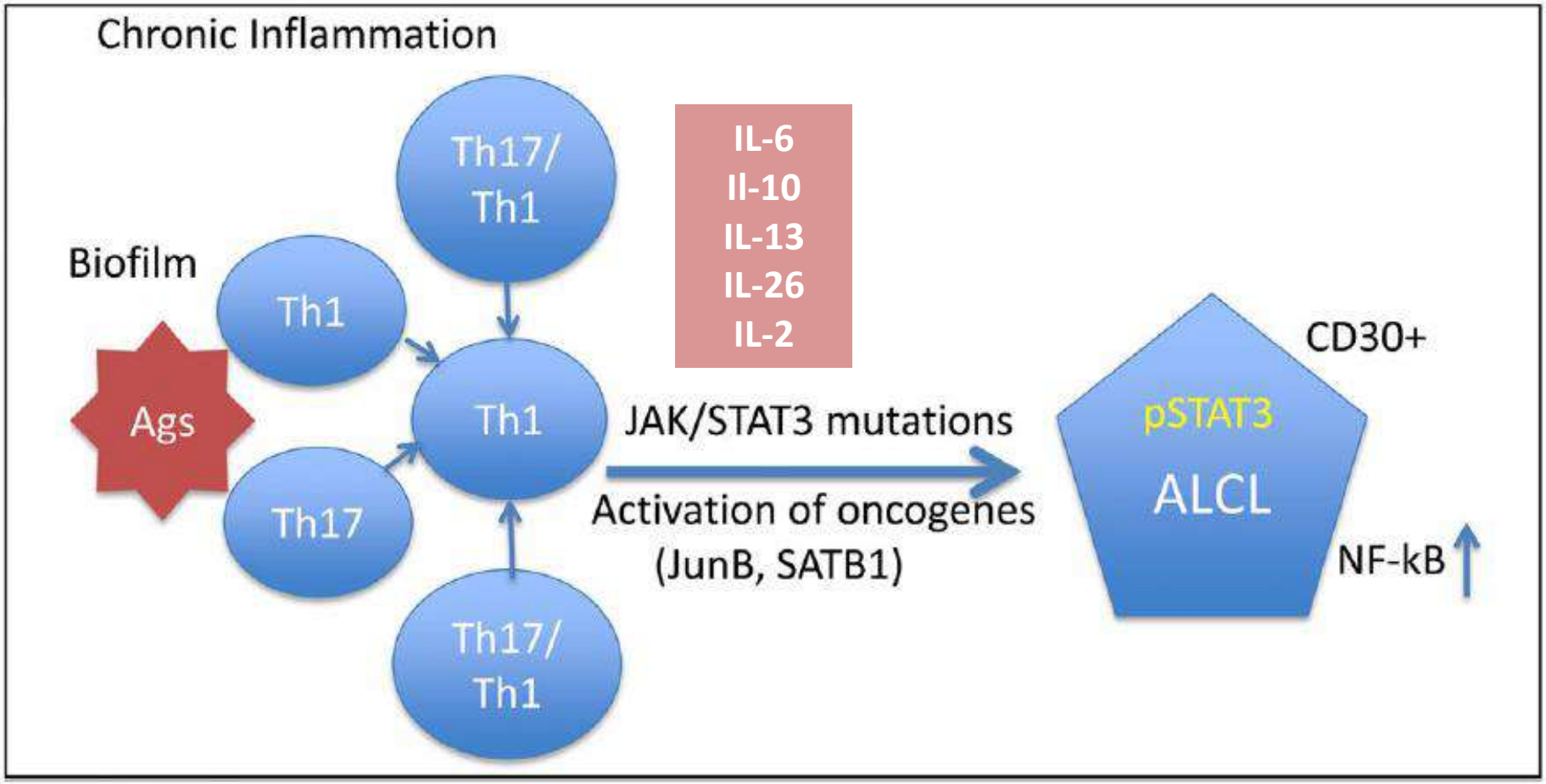


Figure 13. Working hypothesis for progression of immune responding T lymphocytes to BIA-ALCL.

Aesthetic Surgery Journal Advance Access published March 15, 2016

Breast Surgery

Special Topic

Biomarkers Provide Clues to Early Events in the Pathogenesis of Breast Implant-Associated Anaplastic Large Cell Lymphoma

Marshall E. Kadin, MD; Anand Deva, MD; Haiying Xu, BS; John Morgan, PhD; Pranay Khare, PhD; Roderick A.F. MacLeod, PhD; Bruce W. Van Natta, MD; William P. Adams Jr., MD; Garry S. Brody, MD; and Alan L. Epstein, MD, PhD

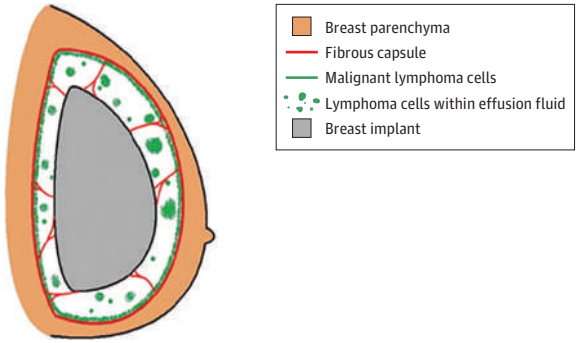
Presentation Outline

- ✓ Epidemiology and correlation with implants
- ✓ Pathogenetic hypothesis
- ✓ Clinical Presentation
- ✓ Evaluation exams and diagnosis
- ✓ Staging
- ✓ Treatment

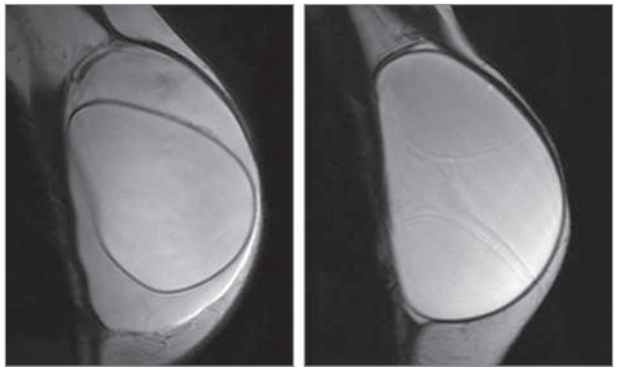
Clinical Presentation

Figure 1. Assessment of Patients With Late Peri-implant Seromas

A Schematic representation



B Affected breast (left) and unaffected breast (right)



C Affected breast axillary loculated (left), medial (middle), and inferior (right) fluid collection

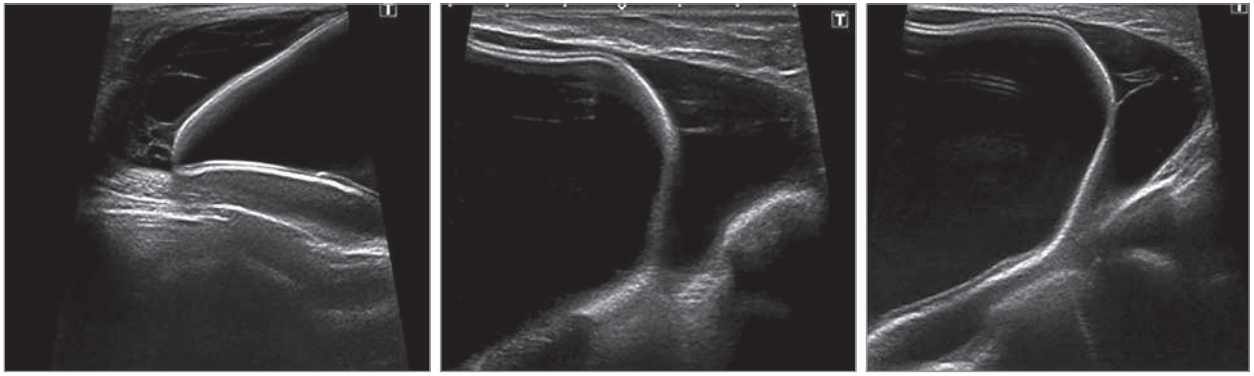
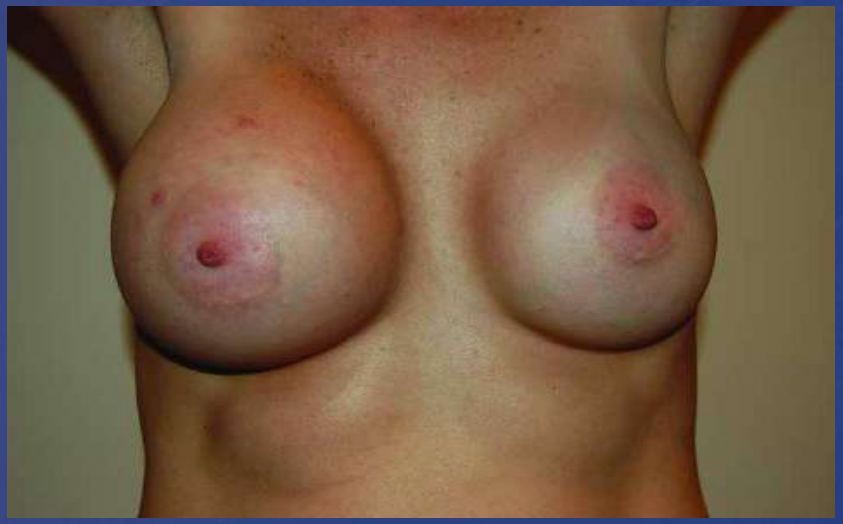


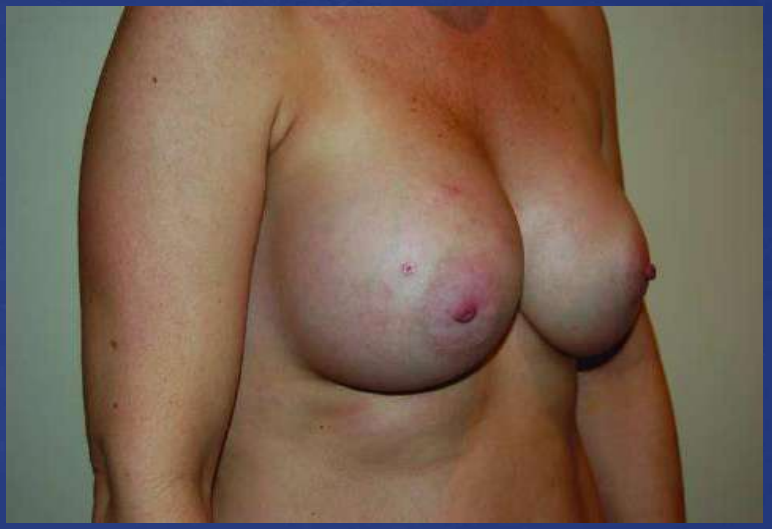
Table 1. Clinicopathological Features of 95 Patients With Breast Implant–Associated Anaplastic Large Cell Lymphoma Included in the Systematic Review

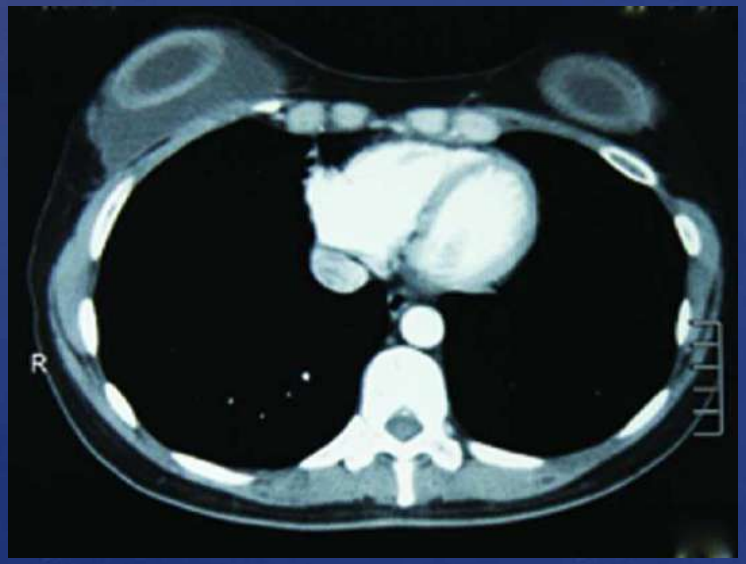
Variable	Value
Age at onset, mean, y (n = 94)	51
Time to onset, y (n = 85)	10
Type of surgery, No./total No. (%)	
Reconstruction	43/80 (54)
Cosmetic	37/80 (46)
Type of implant, No./total No. (%)	
Saline	31/80 (39)
Silicone	49/80 (61)
Initial presentation, No./total No. (%)	
Seroma	55/83 (66)
Mass	7/83 (8)
Both seroma and mass	6/83 (7)
Other	15/83 (18)

Leberfinger AN et al JAMA surgery 2017

Without tumor mass and effusion-associated

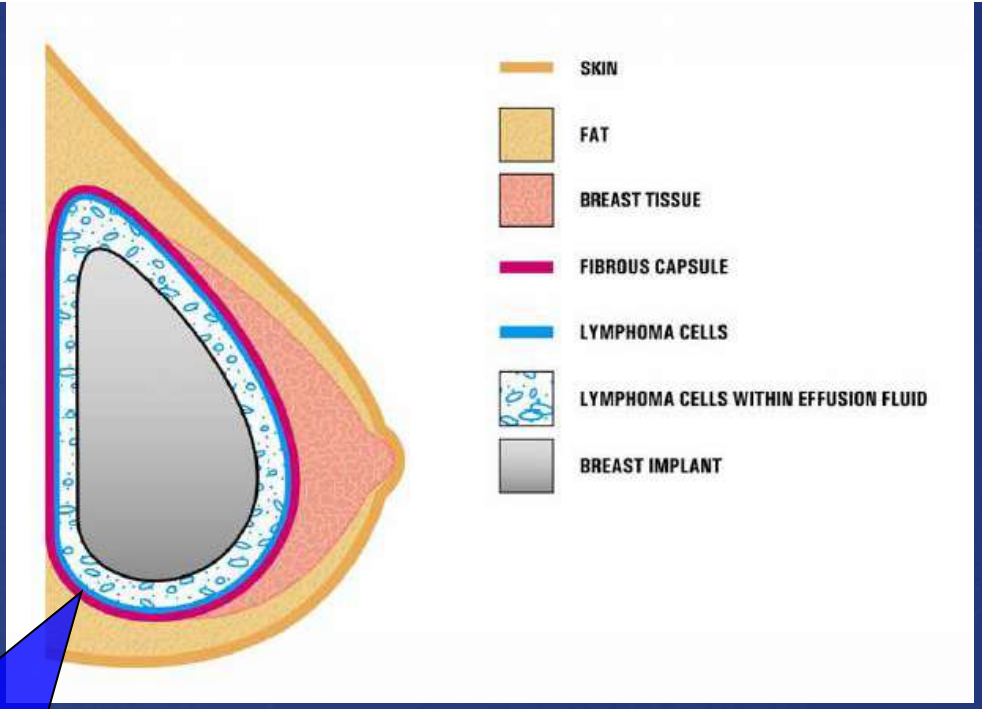


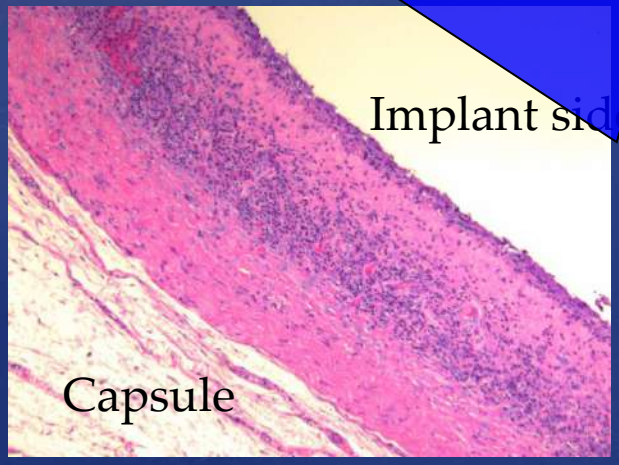


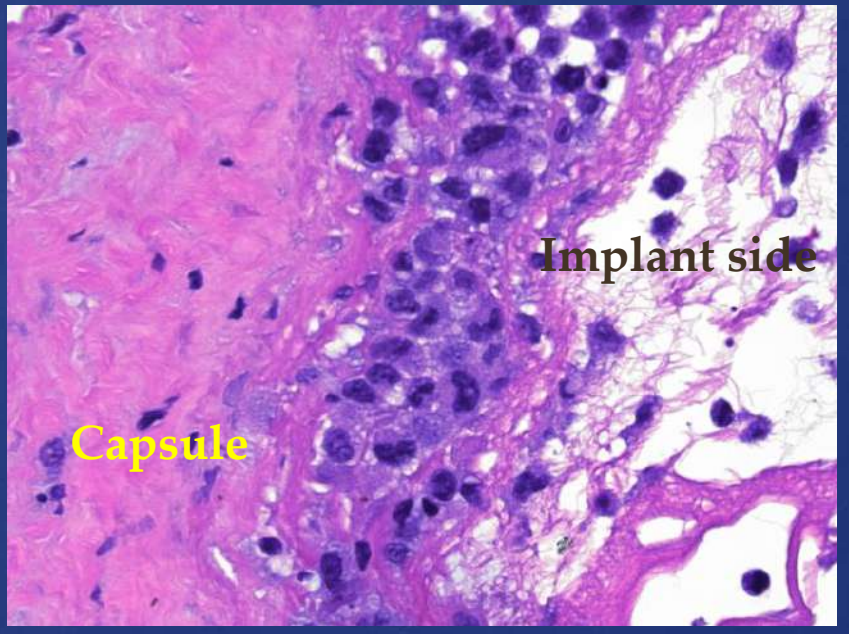


Thompson et al. 2010. Hematologica

Effusion-associated

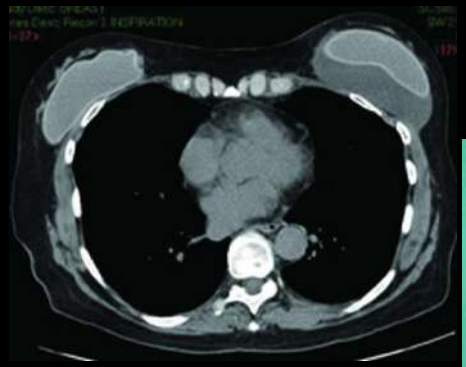


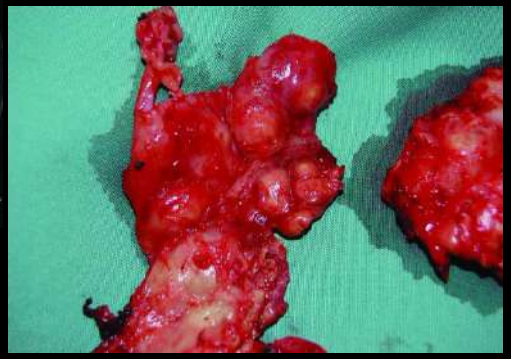


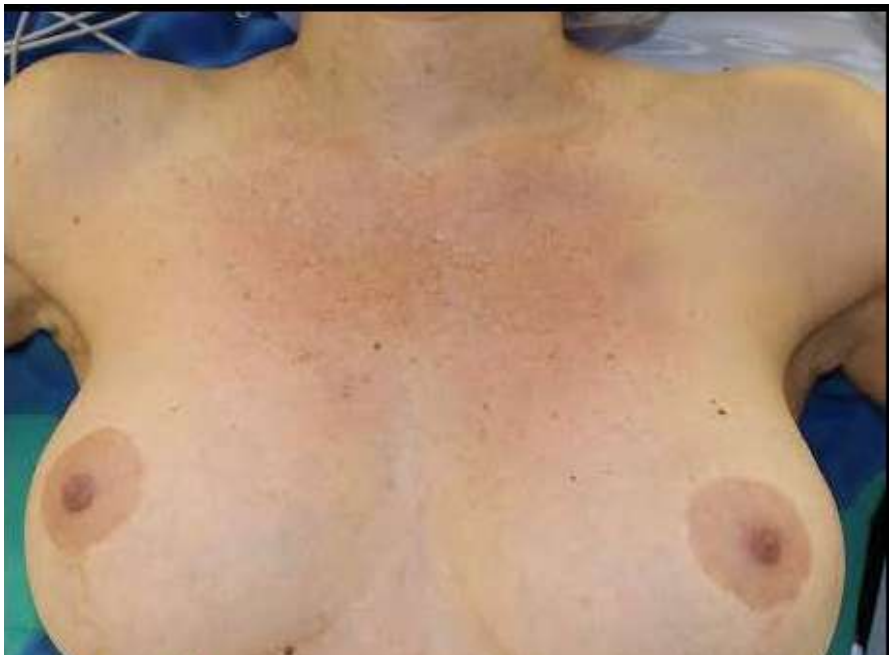


Thompson et al. 2010. Hematologica

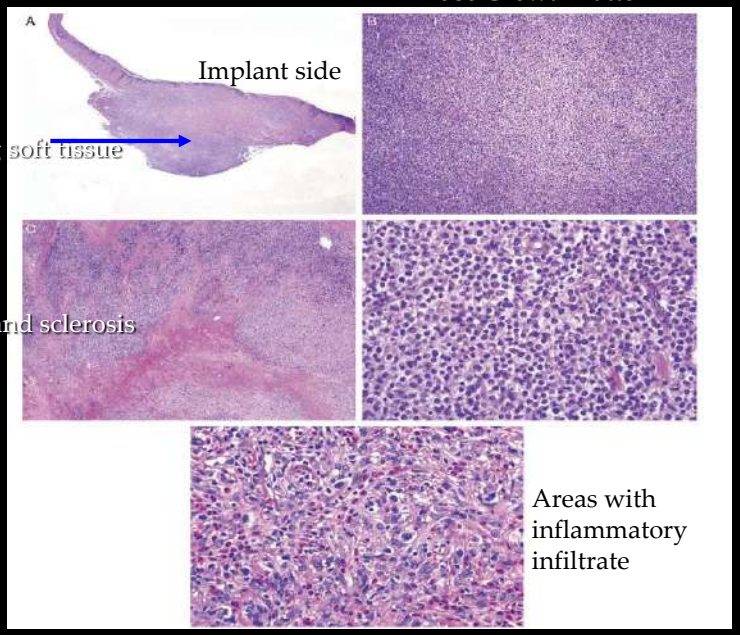
With tumor mass



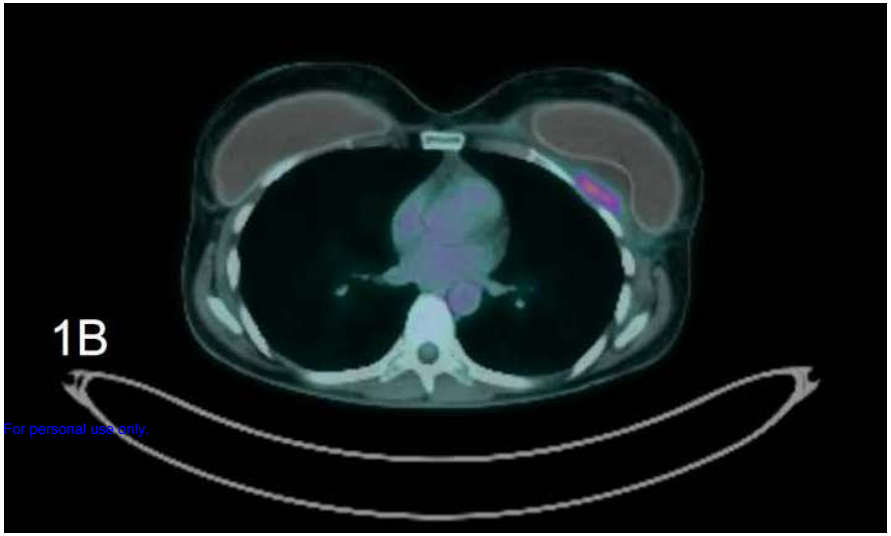




With tumor mass



Am J Surg Pathol • Volume 36, Number 7, July 2012



Mehta-Shah N et al Blood 2018

Clinical Presentation

- ✓ **60-80%** delayed (> 1 year) persistent seroma ± breast swelling, asymmetry or pain. 9-13% of delayed seroma are BIA-ALCL
- ✓ **10-20%** breast mass through the scar capsule around the implant ± seroma. A breast parenchima mass apart from the capsule is not a BIA-ALCL
- ✓ **10-15%** axillary lymphoadenopathy
- ✓ **<10%** Cutaneous lesions (erythema,cutaneous papules), supraclavicular or distant adenopathies, systemic symptoms
- ✓ **Rare** bilateral cases

Leberfinger AN et al JAMA surgery 2017
Mehta-Shah N et al Blood 2018

Presentation Outline

- ✓ Epidemiology and correlation with implants
- ✓ Pathogenetic hypothesis
- ✓ Clinical Presentation
- ✓ Evaluation exams and diagnosis
- ✓ Staging
- ✓ Treatment

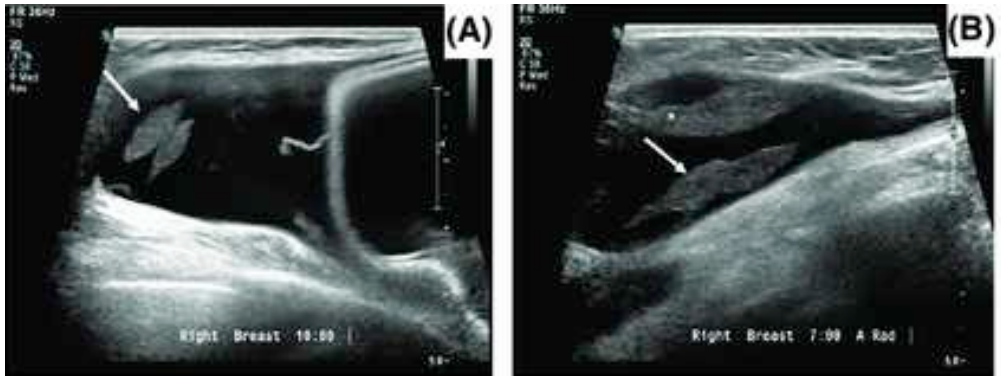
Evaluation of suspected cases

"No screening, testing, or prophylactic surgery is recommended for asymptomatic patients beyond regular mammograms as part of standard breast cancer screening. Patients who have signs or symptoms of possible BIA-ALCL, particularly the development of a seroma more than a year after breast implantation, should undergo evaluation."

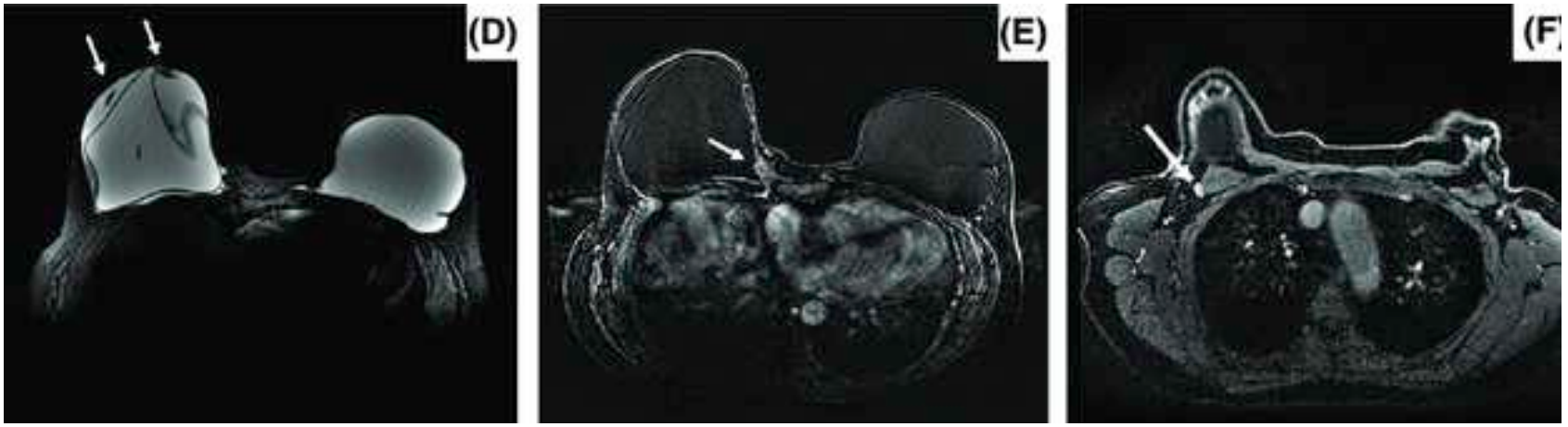
Mehta-Shah N et al Blood 2018

Recommended evaulation exams

Breast ultrasound: **recommended exam** with a sensitivity and specificity for detecting an effusion (84 percent and 75 percent), less sensitive for detecting a mass (46% and 100%)



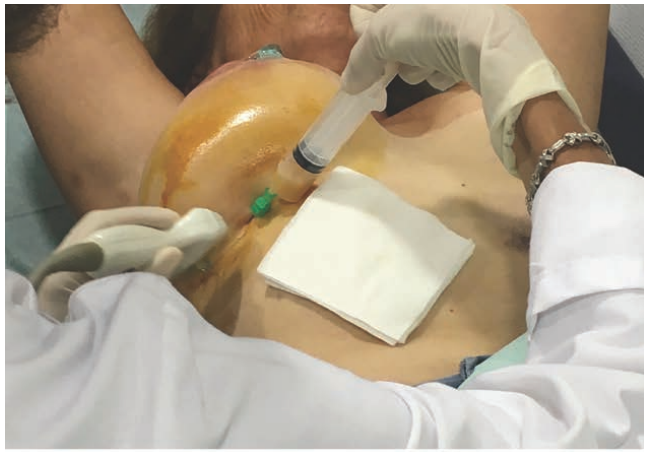
Magnetic Resonance Imaging: **recommended exam in case with suspicion for a mass or ultrasound uncertainty**



Alderluccio JP et al Clin Case reports 2018

Diagnosis

Ultrasound-guided periprostetic fluid fine needle aspiration with cytology and flow cytometry.(20-100 ml)



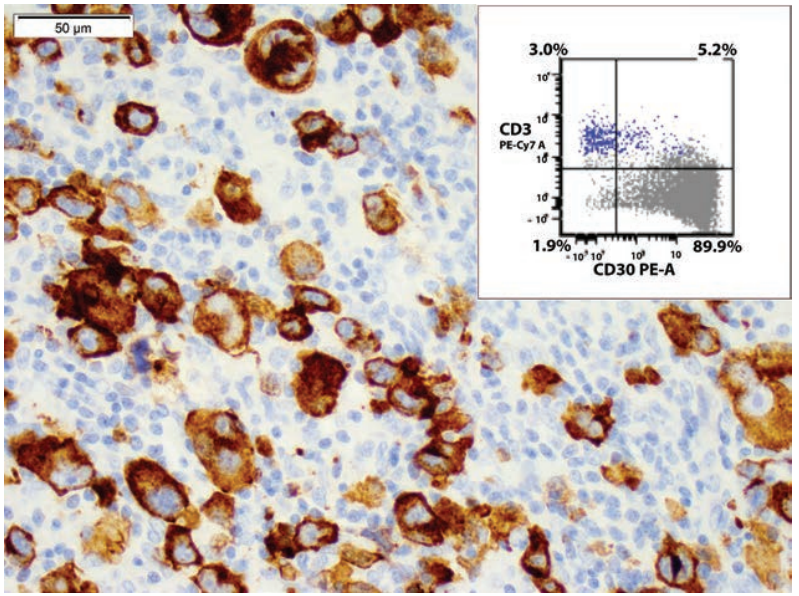


Fig. 4. A malignant effusion in a BIA-ALCL patient demonstrates large pleomorphic cells with prominent horseshoe-shaped nuclei, and nuclear folding and strong diffuse CD30 reactivity by immunohistochemistry (CD30 immunohistochemistry with hematoxylin counterstain, original magnification, × 1000). *Inset* demonstrates a single T-cell population on flow cytometry. Positive cytology and a diffuse expression of CD30 are required for diagnosis.

Clemens MW et al, Plast Recontsr Surg 2018

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Breast implant related Anaplastic Large Cell Lymphoma presenting as late onset peri-implant effusion

Trevor J. Smith [a], Reena Ramsaroop [b,*]

[a] The Breast Centre Ltd, Suite 2, Ascot Integrated Hospital, 90 Greenlane Rd, Remuera, Auckland, New Zealand
[b] Diagnostic Medical Laboratory, 10 Harrison Road, Ellerslie, Auckland, New Zealand

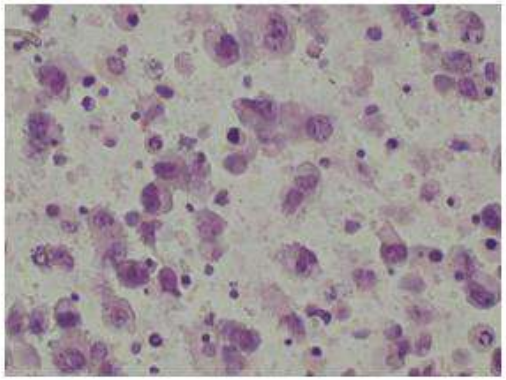


Fig. 1. H&E ×400. Cell block preparation showing discohesive, pleomorphic lymphoid

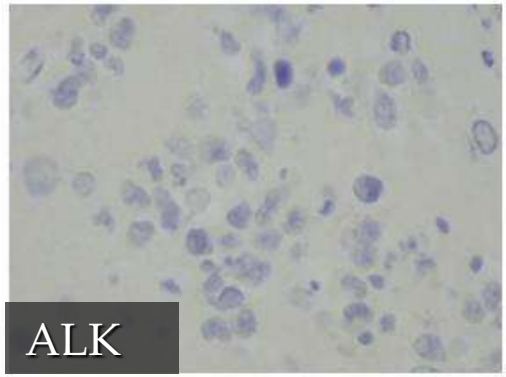
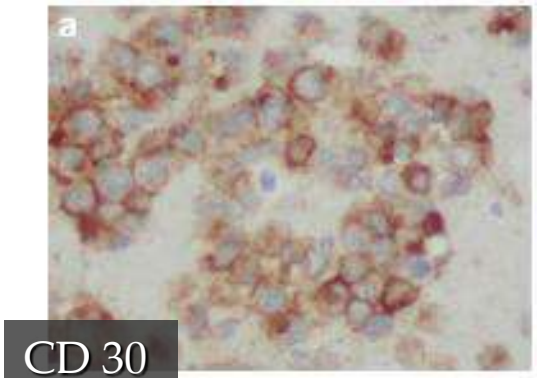
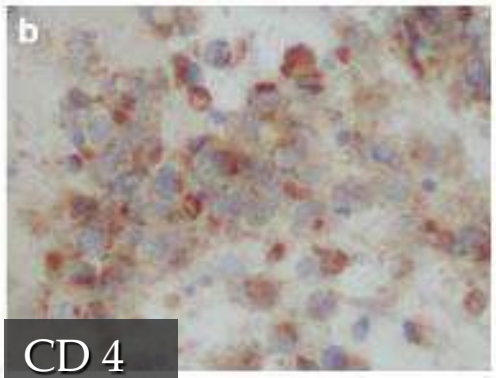


Fig. 3. IHC ×400. ALK1 – malignant lymphoid cells – negative

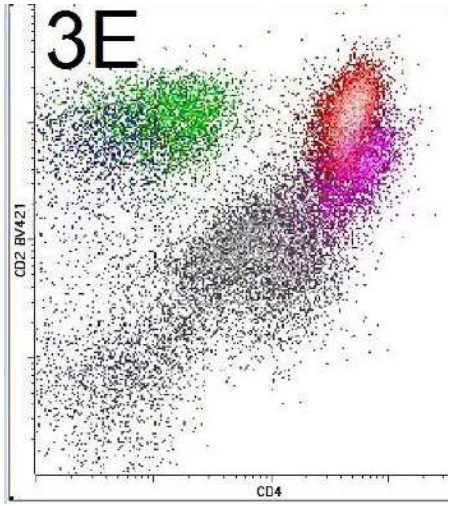


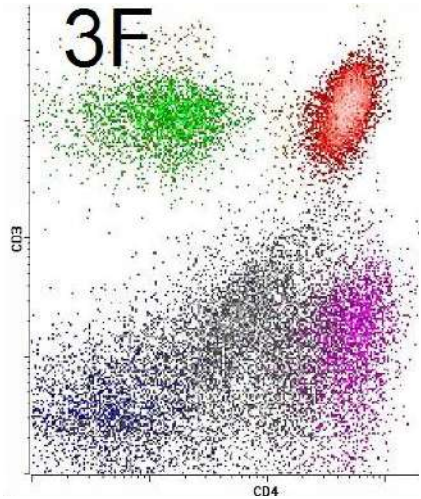


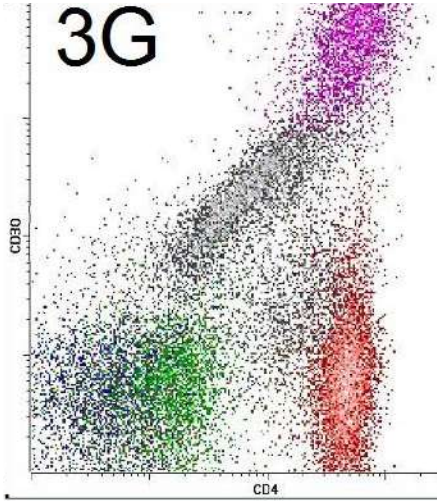
<u>Important:</u>
The malignant cells may be only on the effusion

Immunoistochemistry and flow cytometry

- CD30+ in all (n=64) cases,
- ALK and EBER negative in all (n=56 and 25 respectively) tested cases.
- CD3+ 15 of 62 (24%) cases
- CD4+ 43 of 61 (70%),
- CD8+ 6 of 57 (11%),
- CD43+ 37 of 46 (80%),
- CD45+ 29 of 49 (59%),
- EMA+ 25 of 42 (60%)
- TIA-1+ 28 of 46 (61%)
- Granzyme-B+ 28 of 47 (60%)
- TCR $\alpha\beta$+ 5 of 24 (21%)
- TCR $\gamma\delta$+ 1 of 23 (4%)







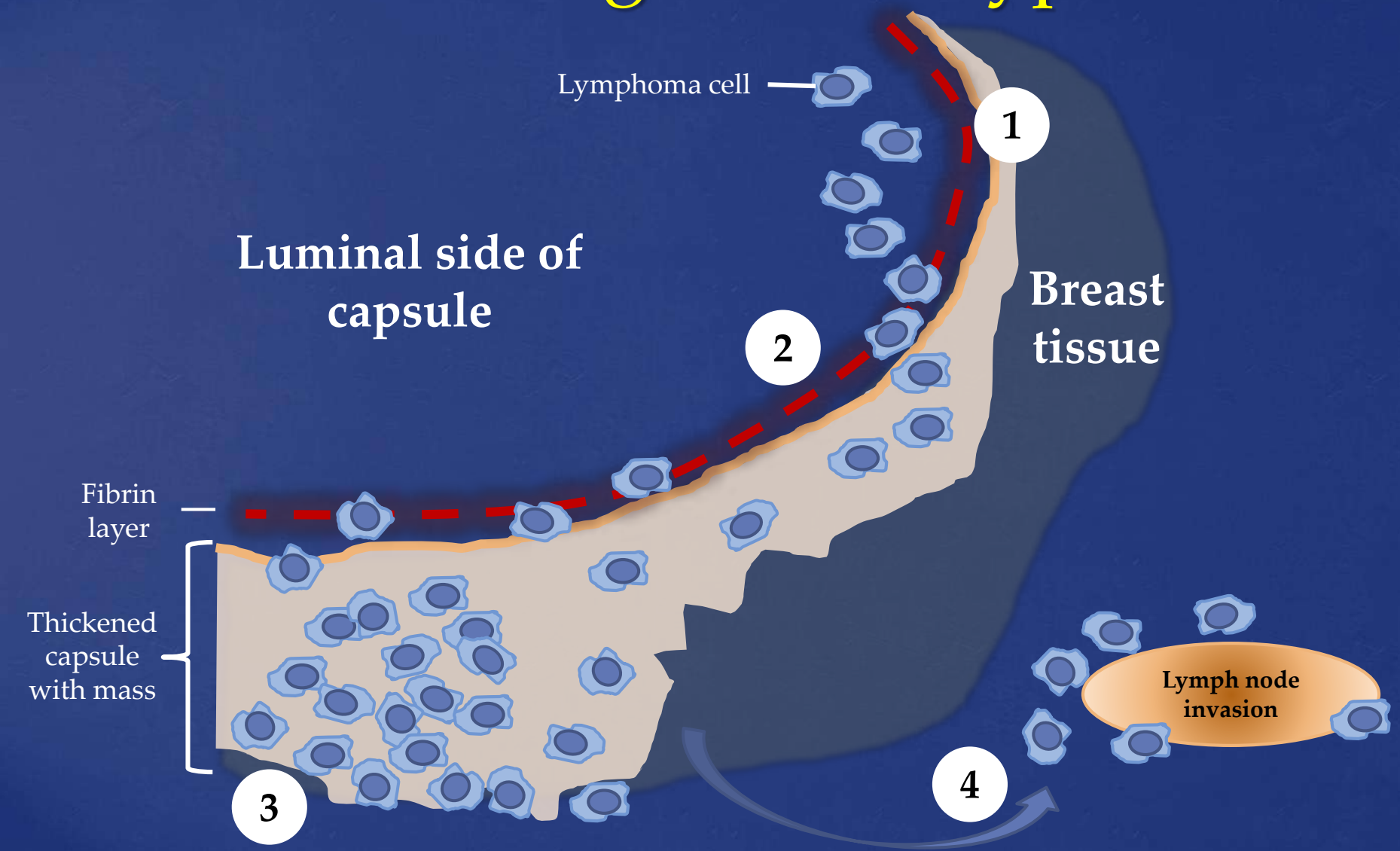
Lopes et al. Comprehensive Immunophenotypic Analysis of 64 Cases of Breast Implant-Associated Anaplastic Large Cell Lymphoma Shows an Activated Cytotoxic with Silent T-Cell Receptor Pattern

Mehta-Shah N et al Blood 2018

Presentation Outline

- ✓ Epidemiology and correlation with implants
- ✓ Pathogenetic hypothesis
- ✓ Clinical Presentation
- ✓ Evaluation exams and diagnosis
- ✓ Staging
- ✓ Treatment

Solid Tumor Progression Hypothesis



BIA-ALCL behaves like a SOLID Tumor (like lung or breast cancer) and therefore treated surgically **(ALSO LIKE HODGKIN AND pcALCL)**

BIA-ALCL specific TNM staging system

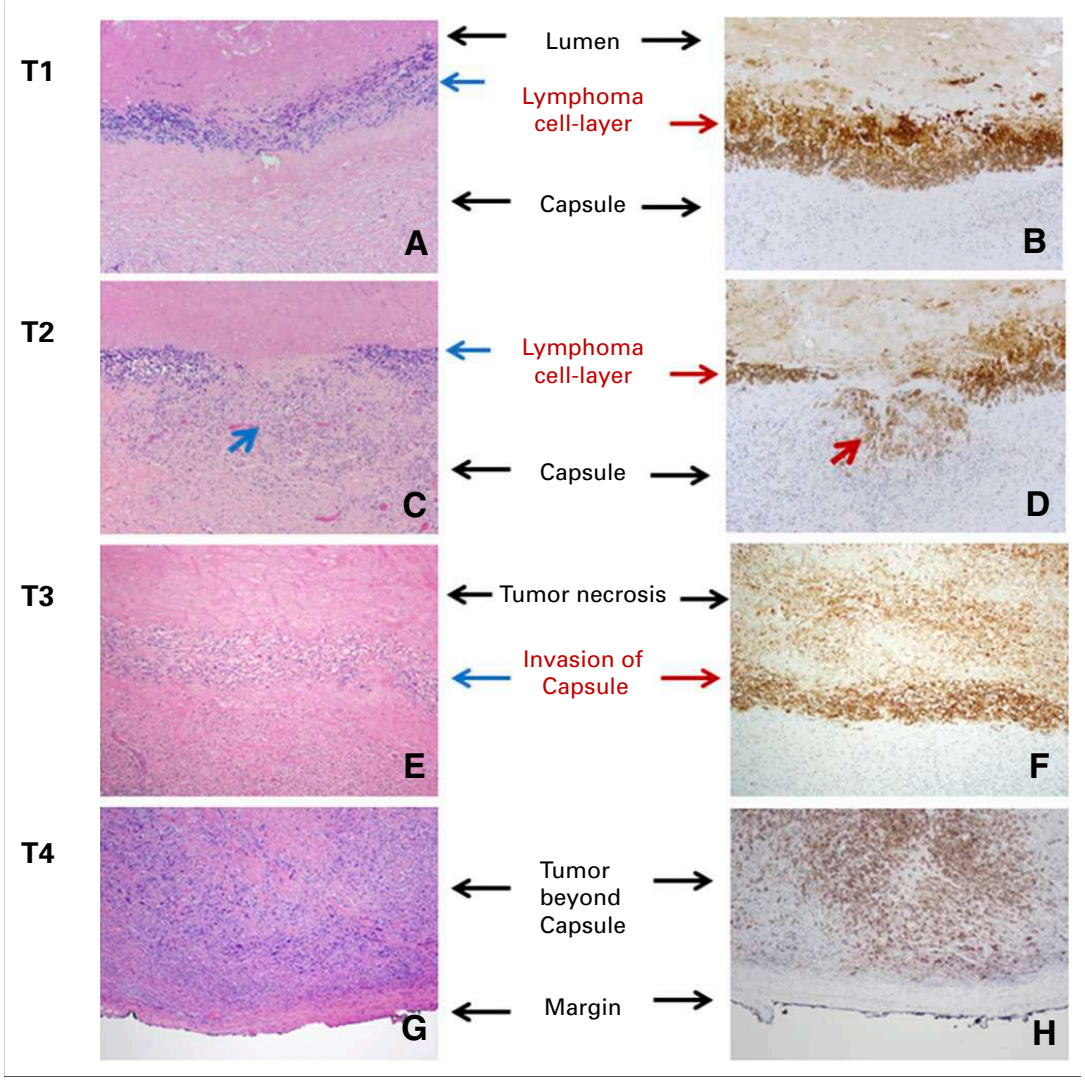


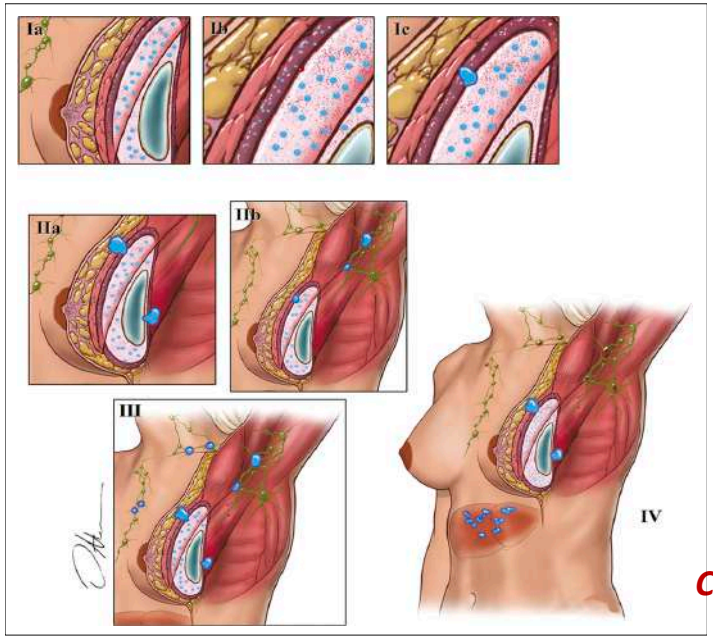
Fig 1. Pathologic T staging. (A and B) T1: lymphoma cells confined to the effusion or a layer on the luminal side of the capsule; (C and D) T2: lymphoma cells superficially infiltrate the luminal side of the capsule. Arrows indicate the areas of invasion; (E and F) T3: clusters or sheets of lymphoma cells infiltrate into the thickness of the capsule; and (G and H) T4: lymphoma cells infiltrating beyond the capsule, into the adjacent soft tissue or breast parenchyma. Left column, hematoxylin and eosin stain; right column, CD30 immunohistochemistry; magnification, ×100.

Clemens MW et al, J Clin Oncol 2015

BIA-ALCL specific TNM staging system

Table 1. BIA-ALCL Tumor, Lymph Node, and Metastasis (TNM) Staging and Stages. Adapted from Clemens et al.[5]

Staging				
Tumor size	**T1**	**T2**	**T3**	**T4**
T	Confined to effusion	Early capsule invasion	Mass aggregate, confined to capsule	Tumor locally invasive out of capsule
Lymph Nodes	N0	N1	N2	
N	No lymph node involvement	One regional lymph node	Multiple regional lymph nodes	
Metastasis	M0	M1		
M	No distant spread	Other organs/distant sites		
Stages				
Stage IA: T1N0M0		Stage IIA: T4N0M0		Stage III: TanyN2M0, T4N1M0
Stage IB: T2N0M0		Stage IIB: T1-3N1M0		Stage IV: TanyNanyM1
Stage IC: T3N0M0				



Clemens MW et al, Aesthet Surg J 2017
Clemens MW et al J Clin Oncol 2015

BIA-ALCL specific TNM staging system

Reported Stage Presentations Worldwide

Study		Ann Arbor		MDA Solid Tumor TNM Stage						
		IE	IIE	IA	IB	IC	IIA	IIB	III	IV
Brody 2015 (n=173)	USA	89.6	10.4	NR	NR					
Clemens 2016 (n=87)	USA	86.2	13.8	35.6	11.5	13.8	25.3	4.6	9.2	0
Loch-Wilkinson 2017 (n=55)	Australia	96.4	3.6	76.4	0	10.9	9.1	0.0	1.8	1.8
De Boer 2017 (n=32)	Netherlands	81.3	18.8	45.2	NR					
Campanale 2017 (n=22)	Italy	81.8	18.2	68.2	0	4.5	9.0	9.0	0	9.0

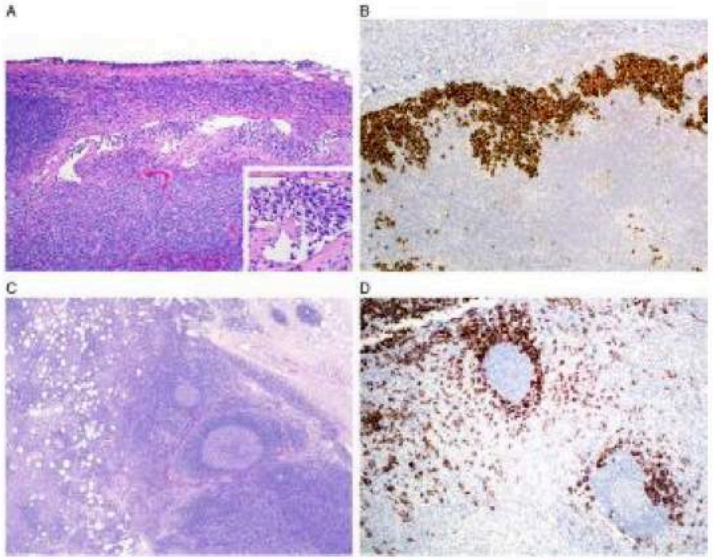
Effusion Only

Infiltrative

By Courtesy of Prince HN, PMcCC Melbourne

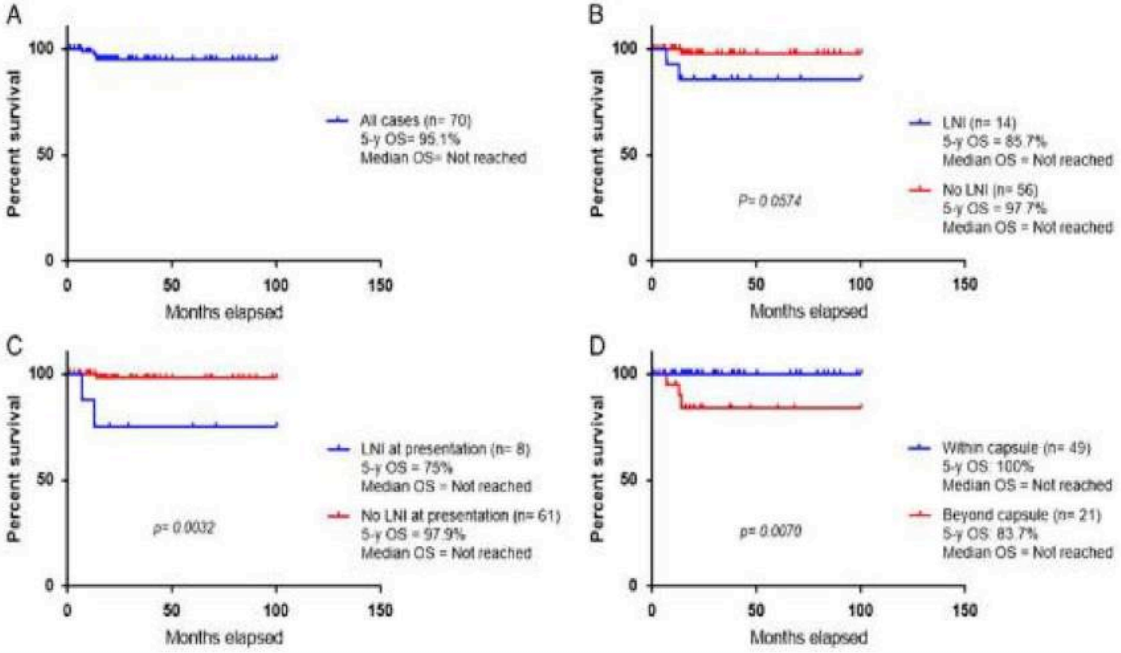
Patterns of Lymph Node Involvement

- 13% of BIA-ALCL Cases
- 85% Axillary, 10% Supraclav, 5% internal mammary
- Mass, LNI portend Worse Prognosis



Clinicopathologic Features and Prognostic Impact of Lymph Node Involvement in Patients With Breast Implant-associated Anaplastic Large Cell Lymphoma

Maria C. Ferrufino-Schmidt, MD,† L. Jeffrey Medeiros, MD,* Hui Liu, MD, PhD,‡ Mark W. Clemens, MD,§ Kelly K. Hunt, MD,‖ Camille Laurent, MD, PhD,¶ Julian Lofts, MD,#*

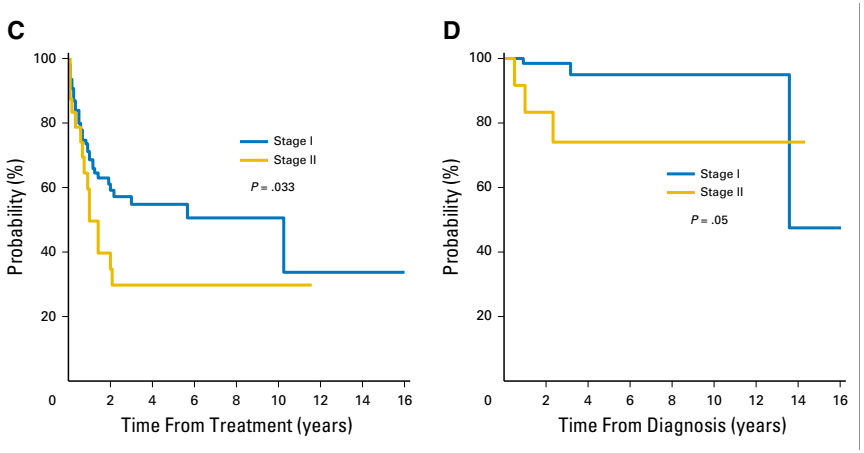


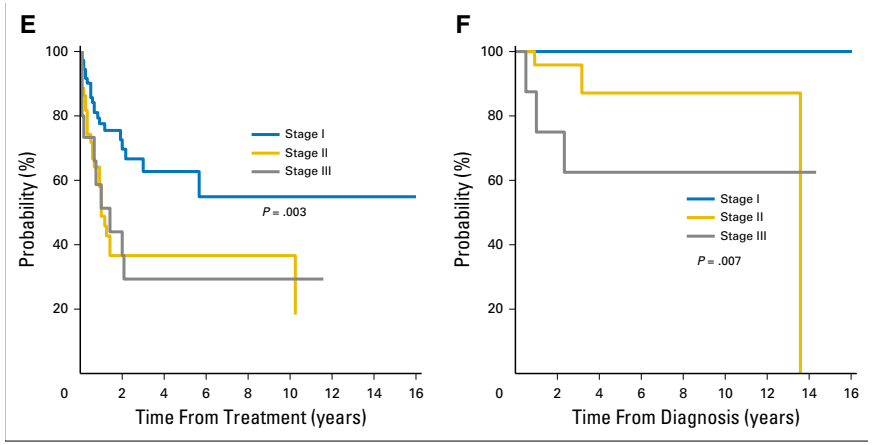
Ferrufino-Schmidt. Clinicopathologic Features and Prognostic Impact of Lymph Node Involvement in Patients With Breast Implant-associated Anaplastic Large Cell Lymphoma. Am J Surg Pathol. 2017

Comparison between Ann Arbor staging and BIA-ALCL specific TNM staging system: 87 patients

Ann Arbor staging
C EFS, D OS

BIA-ALCL staging
E EFS, F OS

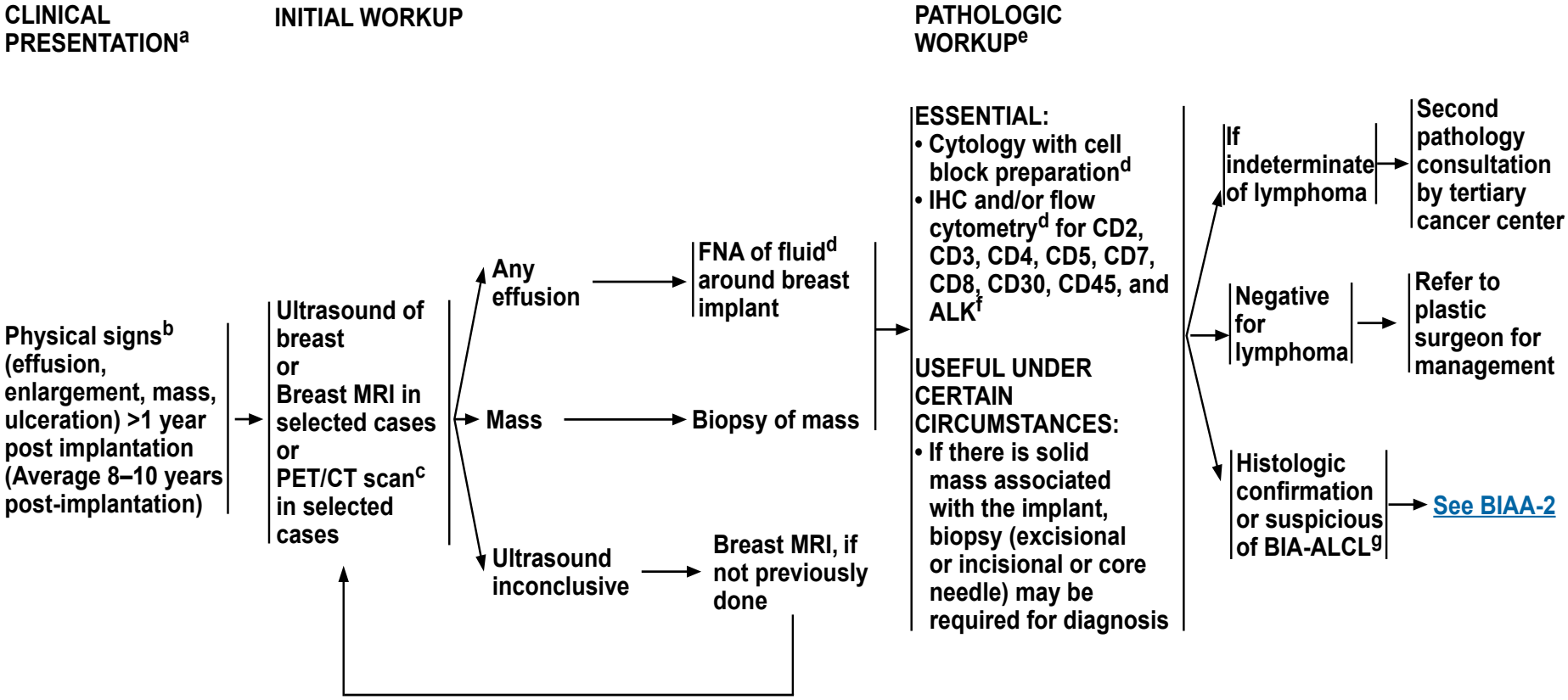




Clemens MW et al, J Clin Oncol 2015

NCCN Guidelines Version 2.2019
Breast Implant-Associated ALCL

NCCN Guidelines Index
Table of Contents
Discussion



Presentation Outline

- ✓ Epidemiology and correlation with implants
- ✓ Pathogenetic hypothesis
- ✓ Clinical Presentation
- ✓ Evaluation exams and diagnosis
- ✓ Staging
- ✓ Treatment

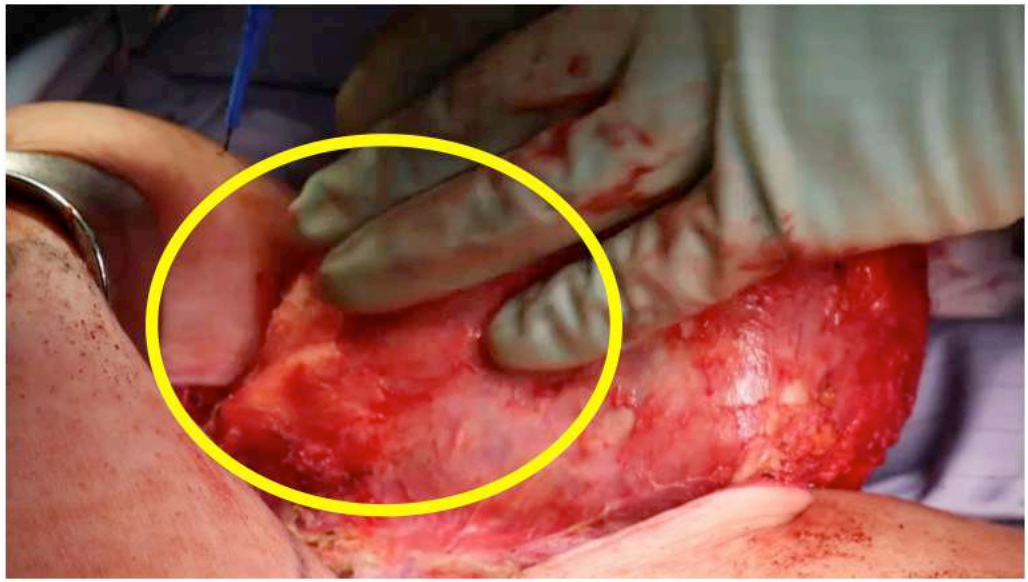
General Treatment key points

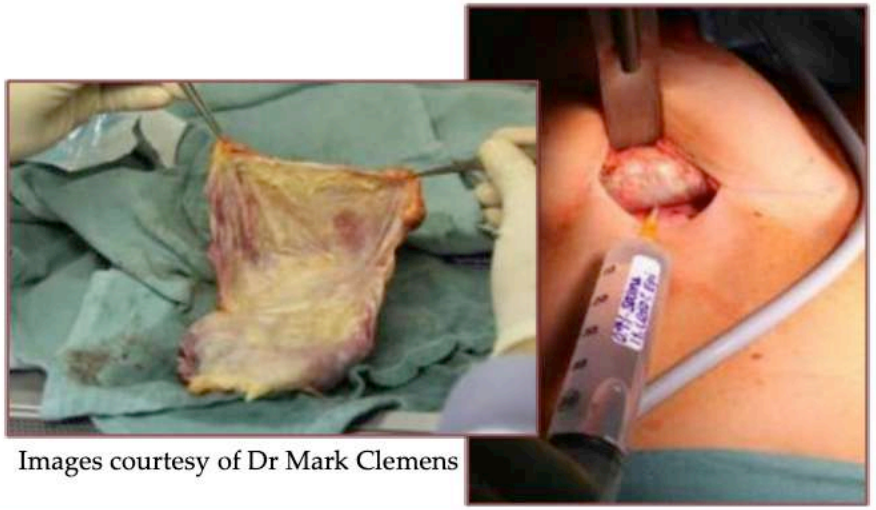
- ✓ **A multidisciplinary team (hematologist, medical oncologist, surgeon, radiation oncologist) is required for optimal mangement60-80%**
- ✓ **PET/CT is mandatory pre-surgery to plan the treatment and surgical approach**
- ✓ **Complete excision of any mass surrounding implant capsule is the optimal treatement and is sufficient for the disease confined to the capsule or resectable chest wall mass**
- ✓ **Mastectomy is not required**
- ✓ **Sentinal lymphnode and fully axillary lymphnode dissection are not useful to reduce recurrence**
- ✓ **Biopsy of any suspicious lymph node is required**
- ✓ **Adjuvant therapy for patients at high risk of recurrence**

Leberfinger AN et al JAMA surgery 2017
Mehta-Shah N et al Blood 2018

Total capsulectomy implant removal

- Oncologic technique[1]
- Orientation sutures
- Surgical clips in tumor bed
- Excision of suspicious lymph nodes[1]
- Complete resection of capsule, including posterior wall
  - Tumescence may aid in removal of the back wall
- No role for sentinel lymph node biopsy





Images courtesy of Dr Mark Clemens

1. NCCN Guidelines. Breast implant-associated ALCL Version 2.2017.

By Courtesy of Prince HN, PMcCC Melbourne

Treatment approaches in 87 patients

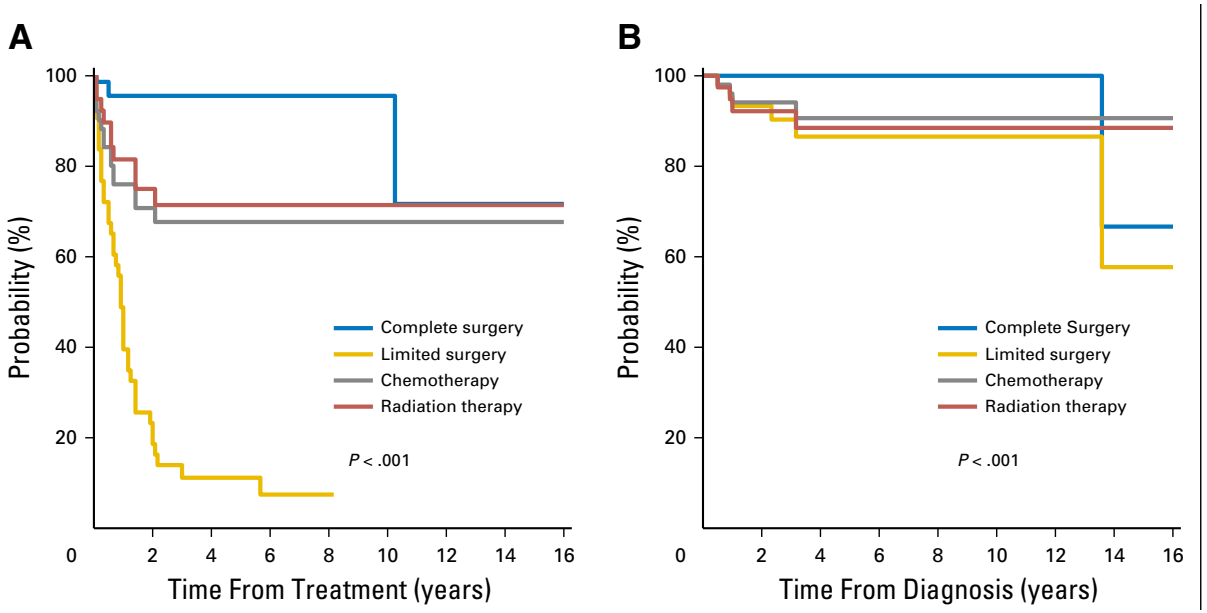


Table 3. Rate of Events After Various Treatment Approaches of Patients With Breast Implant–Associated Anaplastic Large-Cell Lymphoma

Treatment Approach	Event Rate (%) by Time Point		
	1 Year	3 Years	5 Years
Limited surgery (n = 43)	60	89	89
Complete surgery (n = 74)	4	4	4
Radiation therapy (n = 39)	18	28	28
Chemotherapy (n = 51)	24	32	32
Ann Arbor stage			
IE	31	45	45
IIE	50	70	70
TNM stage			
I	22	37	37
II	51	63	63
III	48	71	71

NOTE. The total number of treatment approaches is greater than 87, because some patients received multiple treatment approaches.

Clemens MW et al, J Clin Oncol 2015

Adjuvant therapy

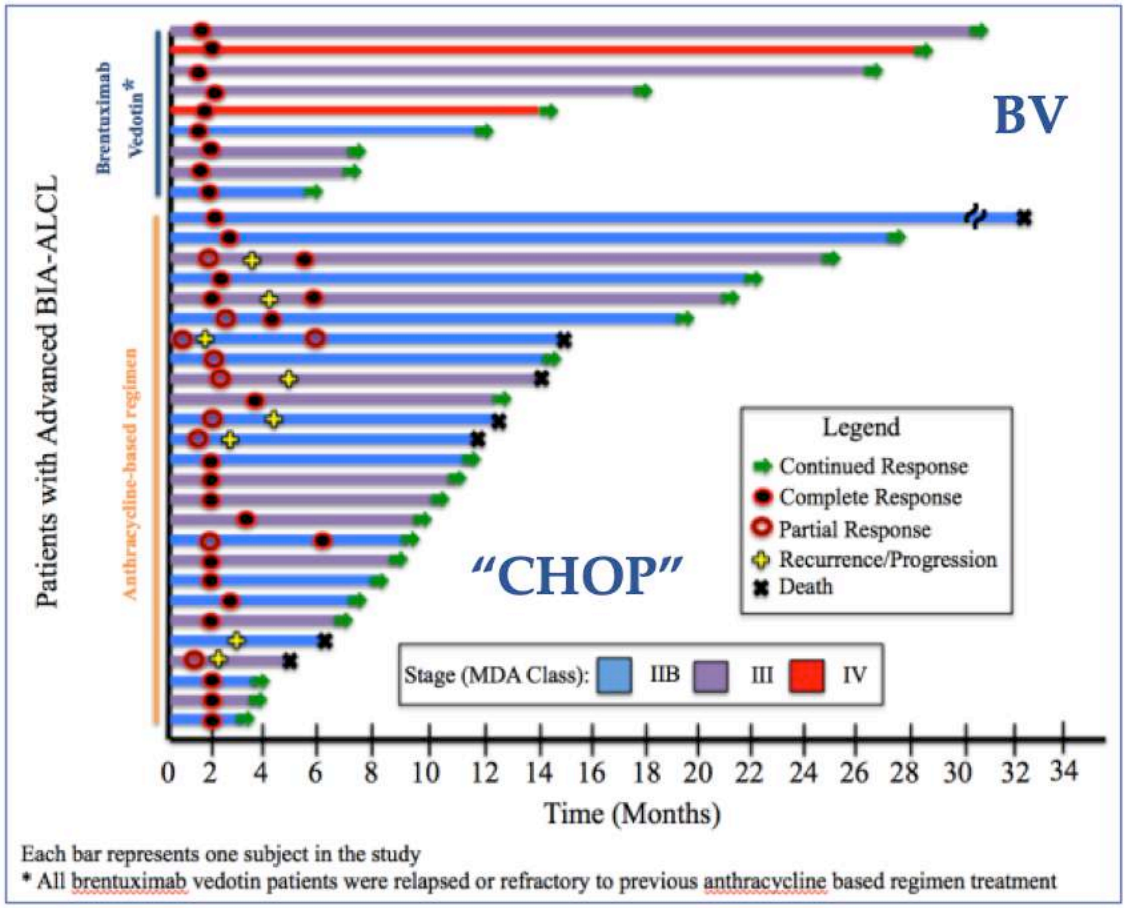
- ✓ **No established approach**
- ✓ **Patients with evidence of disease beyond the capsule (Stage IIA,B, III, IV) have higher risk of progression/ recurrence**
- ✓ **Patients with residual localized disease after surgery: localized radiotehrapy (Gy 24-36) if no previous RT or chemotherapy**
- ✓ **Advanced stage: chemotherapy as nodal ALCL (CHOEP, CHOP, Brentuximab-Vedotin,± Radiotherapy**

Leberfinger AN et al JAMA surgery 2017
Mehta-Shah N et al Blood 2018

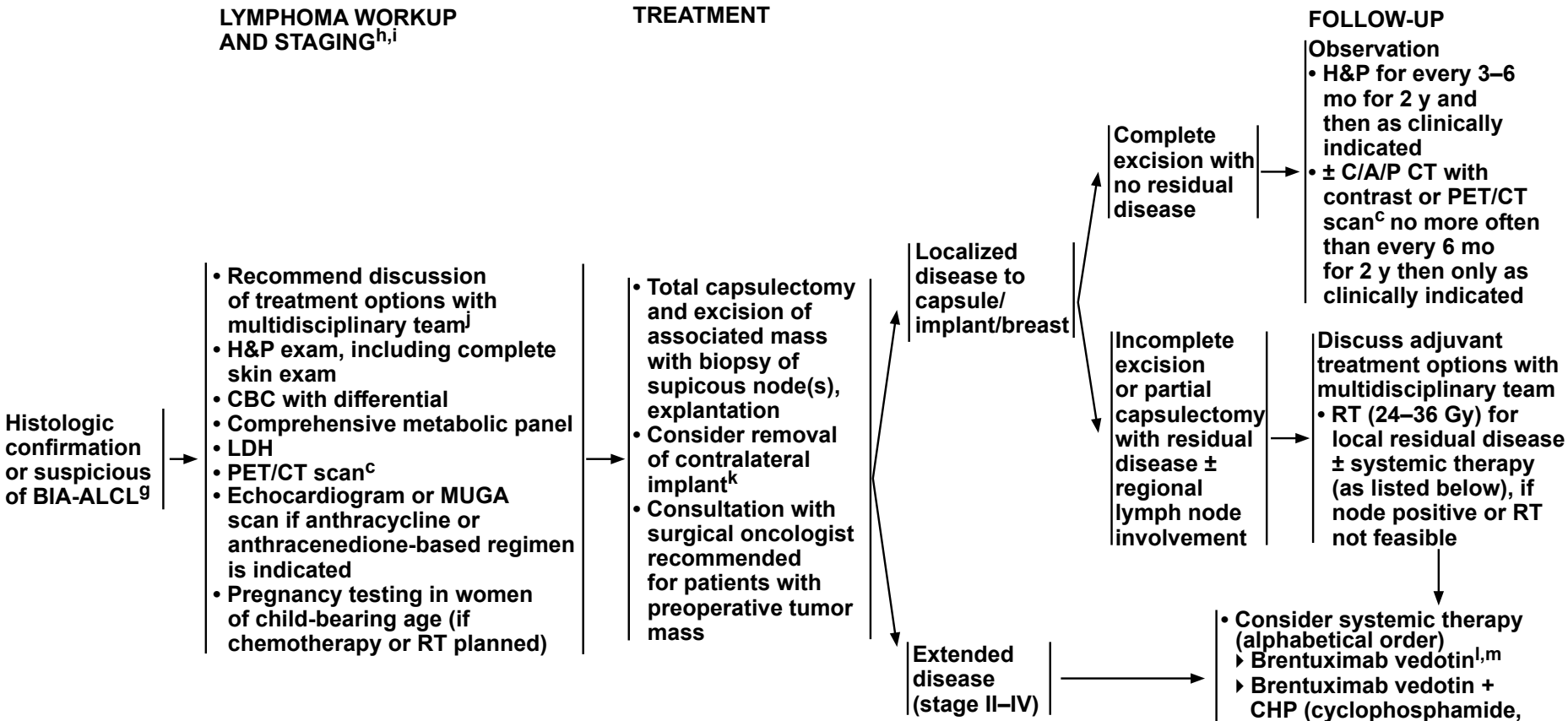
Novel approaches

Brentuximab vedotin

- BIA-ALCL: nine R/R patients treated achieved complete remission
- Complete remission in relapsed and refractory BIA-ALCL with BV
- Versus 32% recurrence rate at 3 years with anthracycline-based regimen

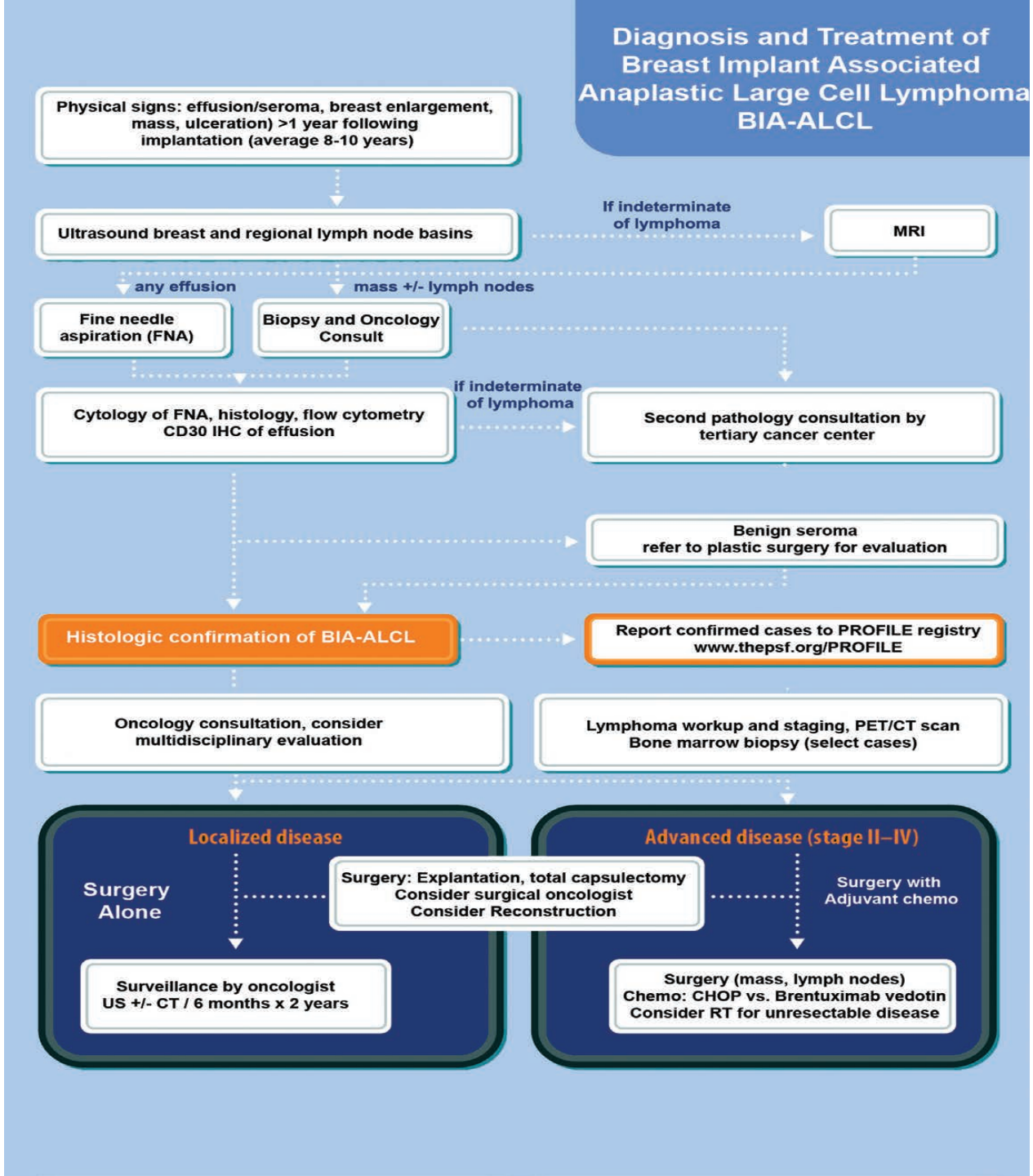


By Courtesy of Prince HN, PMcCC Melbourne



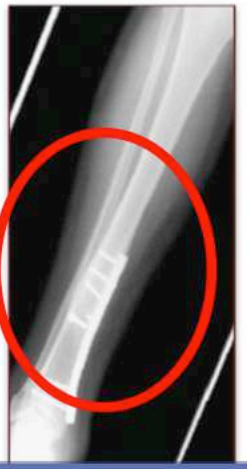
[c]Patients with T-cell lymphomas often have extranodal disease, which may be inadequately imaged by CT. PET scan may be preferred in these instances.
[g]The FDA recommends reporting all BIA-ALCL cases to the PROFILE Registry: www.thepsf.org/PROFILE.
[h]See Proposed TNM Staging for Breast Implant–Associated Anaplastic Large-Cell Lymphoma (BIAA-B).
[i]For BIA-ALCL, bone marrow biopsy is *only* needed in selected cases (eg, extensive disease or unexplained cytopenia).
[j]Eg, oncologist, surgical oncologist, plastic surgeon, hematopathologist.
[k]In approximately 4.6% of cases, lymphoma was found in the contralateral breast (Clemens MW, Medeiros LJ, Butler CE, et al. J Clin Oncol 2016;34:160-168).
[l]Brentuximab vedotin may be appropriate for low burden disease in selected patients.
[m]See Supportive Care (LYMP-B).

See References on BIAA-A


Diagnosis and Treatment of Breast Implant Associated Anaplastic Large Cell Lymphoma BIA-ALCL
Physical signs: effusion/seroma, breast enlargement, mass, ulceration) >1 year following implantation (average 8-10 years)
Ultrasound breast and regional lymph node basins
If indeterminate of lymphoma
MRI
any effusion
mass +/- lymph nodes
Fine needle aspiration (FNA)
Biopsy and Oncology Consult
Cytology of FNA, histology, flow cytometry CD30 IHC of effusion
if indeterminate of lymphoma
Second pathology consultation by tertiary cancer center
Benign seroma refer to plastic surgery for evaluation
Histologic confirmation of BIA-ALCL
Report confirmed cases to PROFILE registry www.thepsf.org/PROFILE
Oncology consultation, consider multidisciplinary evaluation
Lymphoma workup and staging, PET/CT scan Bone marrow biopsy (select cases)
Localized disease
Surgery Alone
Surgery: Explantation, total capsulectomy Consider surgical oncologist Consider Reconstruction
Surveillance by oncologist US +/- CT / 6 months x 2 years
Advanced disease (stage II–IV)
Surgery with Adjuvant chemo
Surgery (mass, lymph nodes) Chemo: CHOP vs. Brentuximab vedotin Consider RT for unresectable disease

Prosthesis-associated?

- Tibial Implant
- Dental implant ALCL[2]
- Chest port ALCL[3]
- Total hip arthroplasties have higher rates of lymphoma[4]
- Shoulder repair ALCL
- Lap Band ALCL

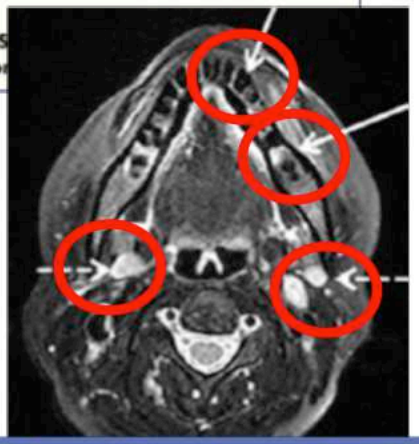


Tibial implant ALCL[1]

Case Report

Mucosal CD30-Positive T-Cell Lymphoproliferative Disorder Arising in the Oral Cavity Following Dental Implants: Report of the First Case

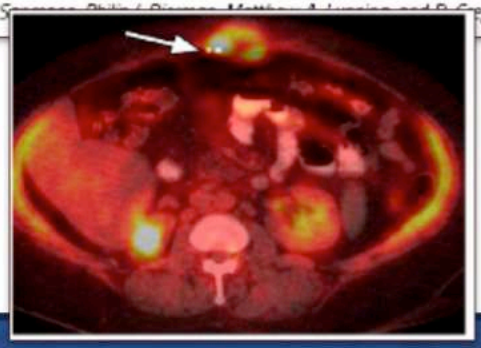
Hye-Jung Yoon, DDS
and Yoon Kyung Jeo



Dental implant ALCL[2]

Bariatric Implant–Associated Anaplastic Large-Cell Lymphoma

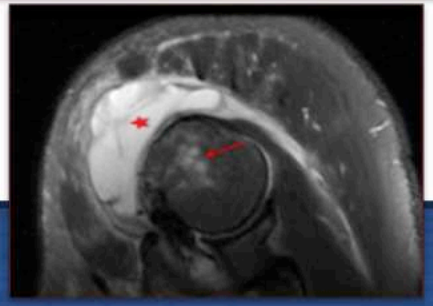
Jayadev Manikkam Umakanthan, Corrigan L. McBride, Timothy Greiner, Ji Yuan, Jennifer S... Gregory Bociek



CASE REPORT

Anaplastic large cell lymphoma masquerading as osteomyelitis of the shoulder: an uncommon presentation

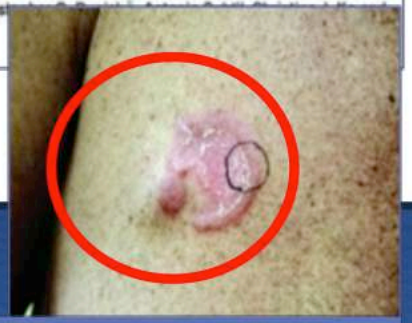
Matthew Tuck,[1,2] Jane Lim,[3] Jose Lucar,[4] Debra Benator[2]



© 2013 by American Society of Clinical Oncology

Development of a Plaque Infiltrated With Large CD30+ T Cells Over a Silicone-Containing Device in a Patient With History of Sézary Syndrome

Anna K. Engberg, Christ...
Michael Girardi



Chest port ALCL[3]

1. Palraj B, et al. J Foot Ankle Surg 2010;49:561–4; 2. Yoon HJ, et al. Int J Surg Pathol 2015;23:656–61; 3. Engberg A, et al. J Clin Oncol 2013;31:e87–e89. 4. Kellogg B et al. Annals Plastic Surgery 2013; 73(4).

Conclusions

- BIA-ALCL is a rare T-cell lymphoma, but its knowledge and timely are required to allow an optimal outcome to the patients
- Symptomatic patients should be evaluated with breast ultrasound and/or NRMI
- Peri-prosthetic effusion later than 1 year after the implantation should be collected and evaluated for CD30 immuoistochemistry and flow-cytometry
- BIAL-ALCL patients should be evaluated by a multidisciplinary team
- BIA-ALCL confined to the capsule can be treated with surgery alone
- Local residual or unresectable disease may be treated with radiation therapy BIA-ALCL localized to the capsule can be treated with surgery alone
- Advanced BIA-ALCL with regional or distant lymph node require adjuvant chemotehrapy