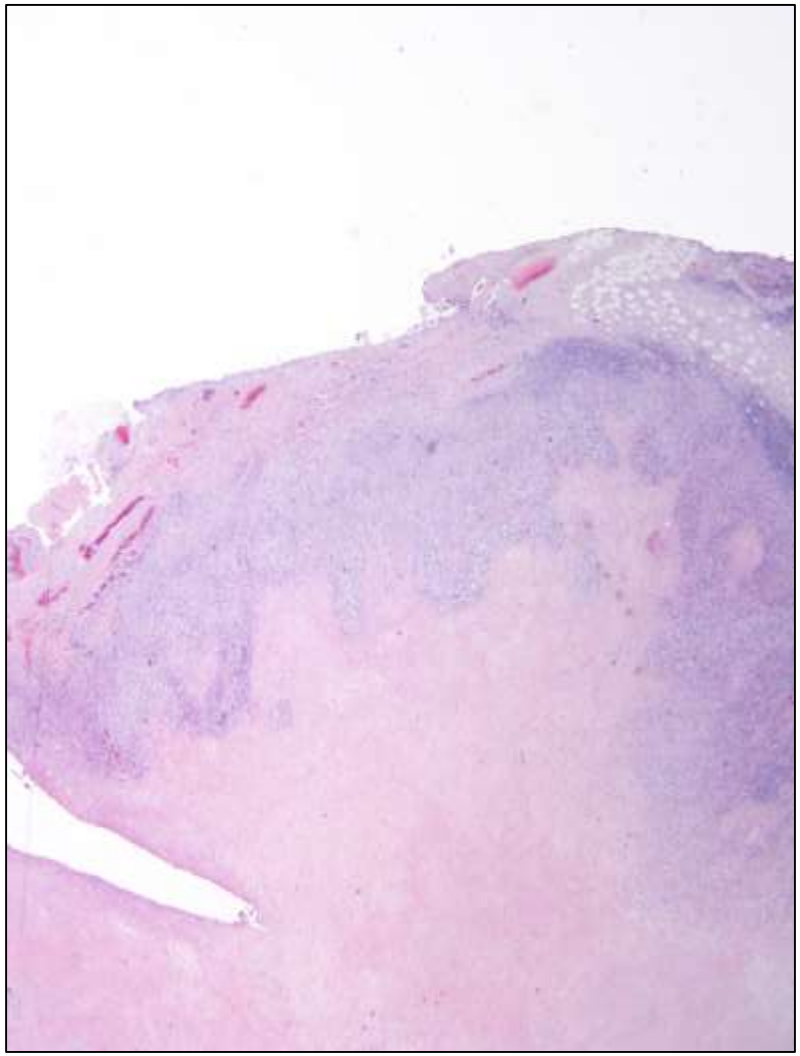
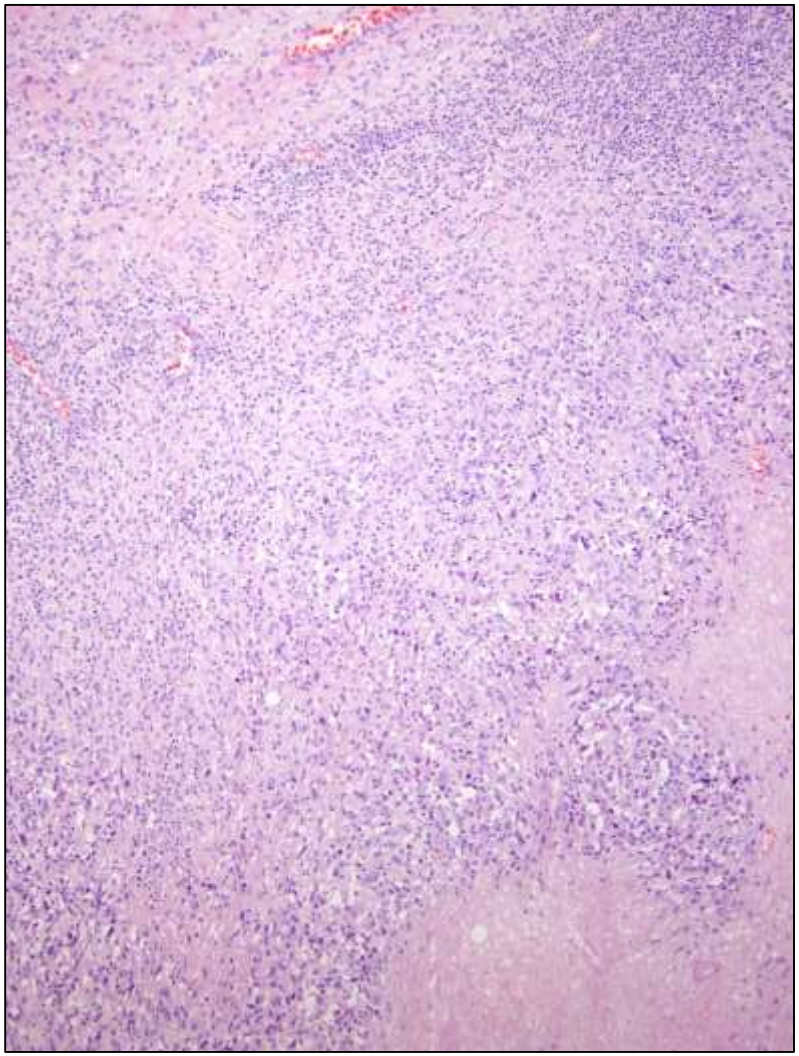
- 72 y/o female
- Breast implant, 27 years previous
- Currently, edema and fluid enlarging breast

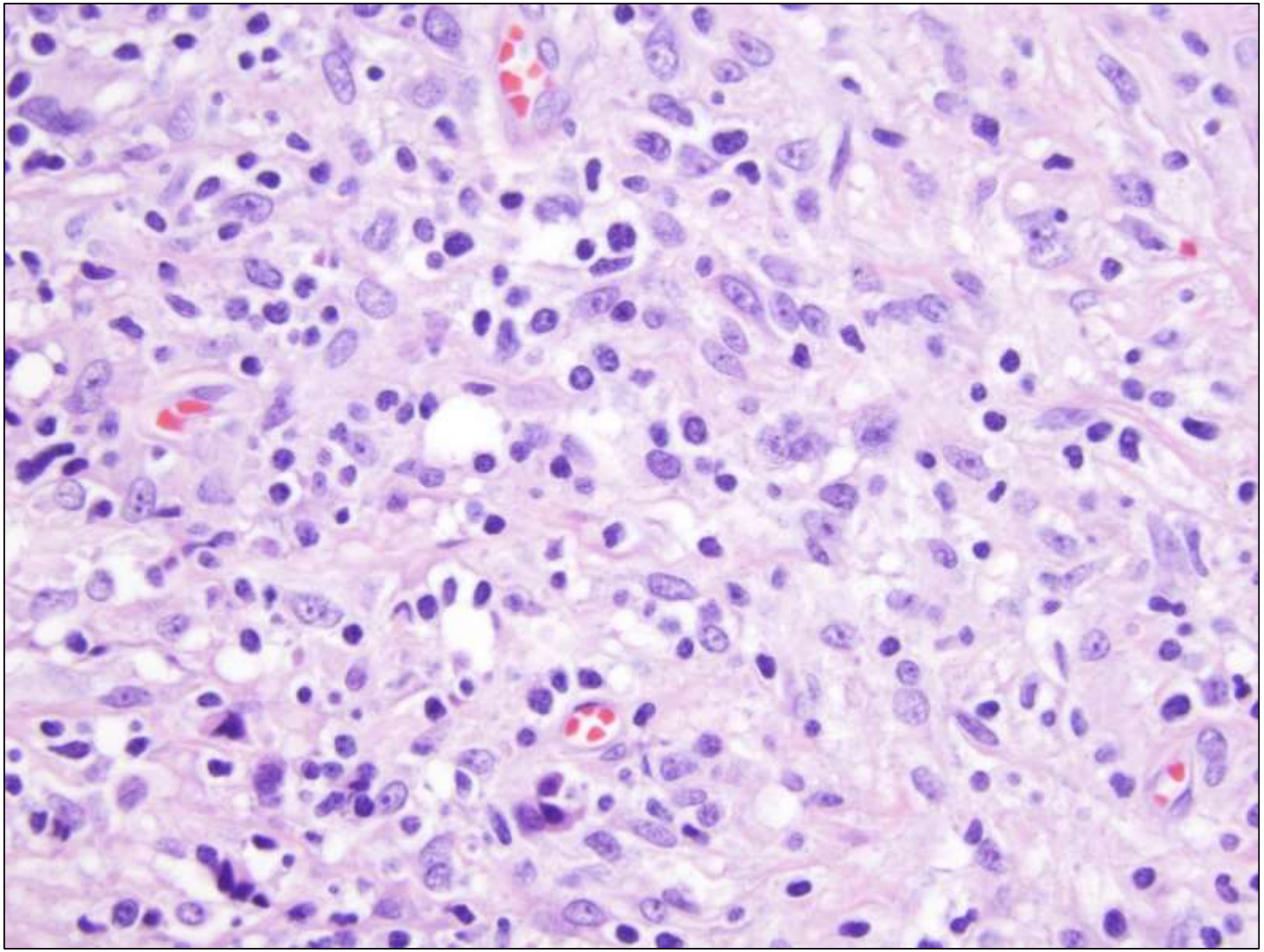
- Breast implant capsule

Breast implant capsule

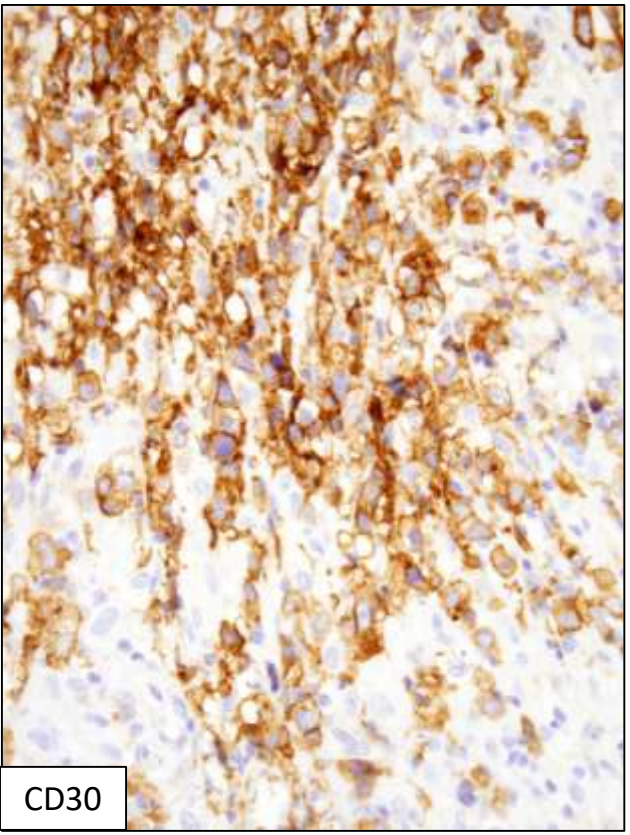


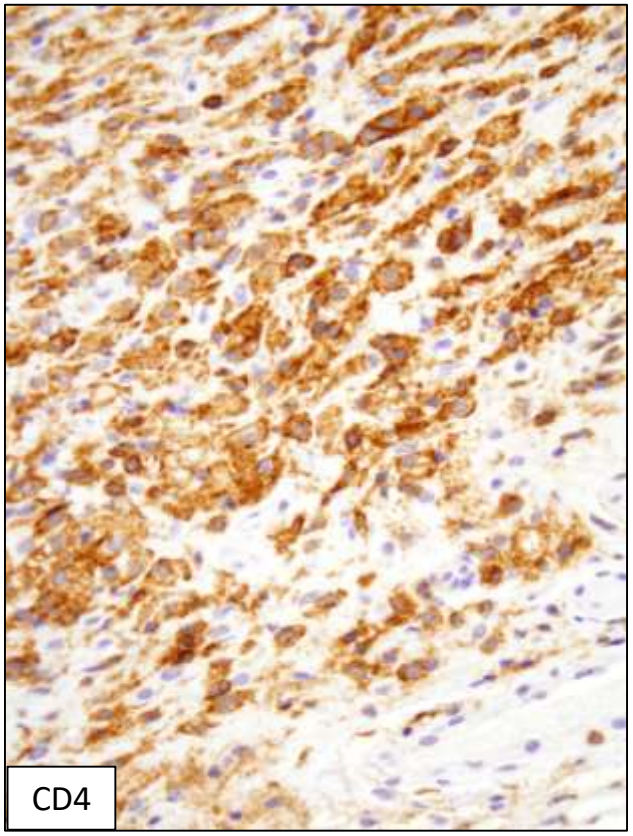


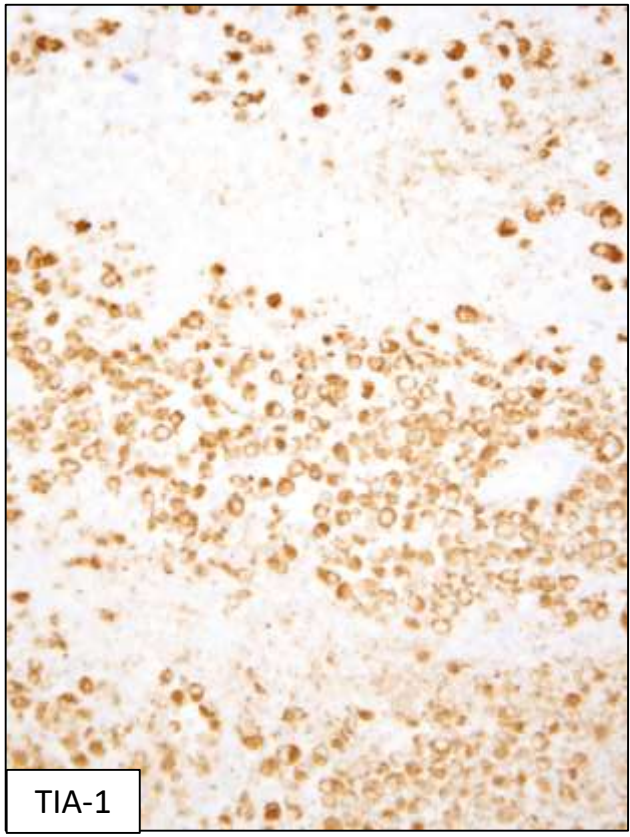
Breast implant capsule



Breast implant capsule





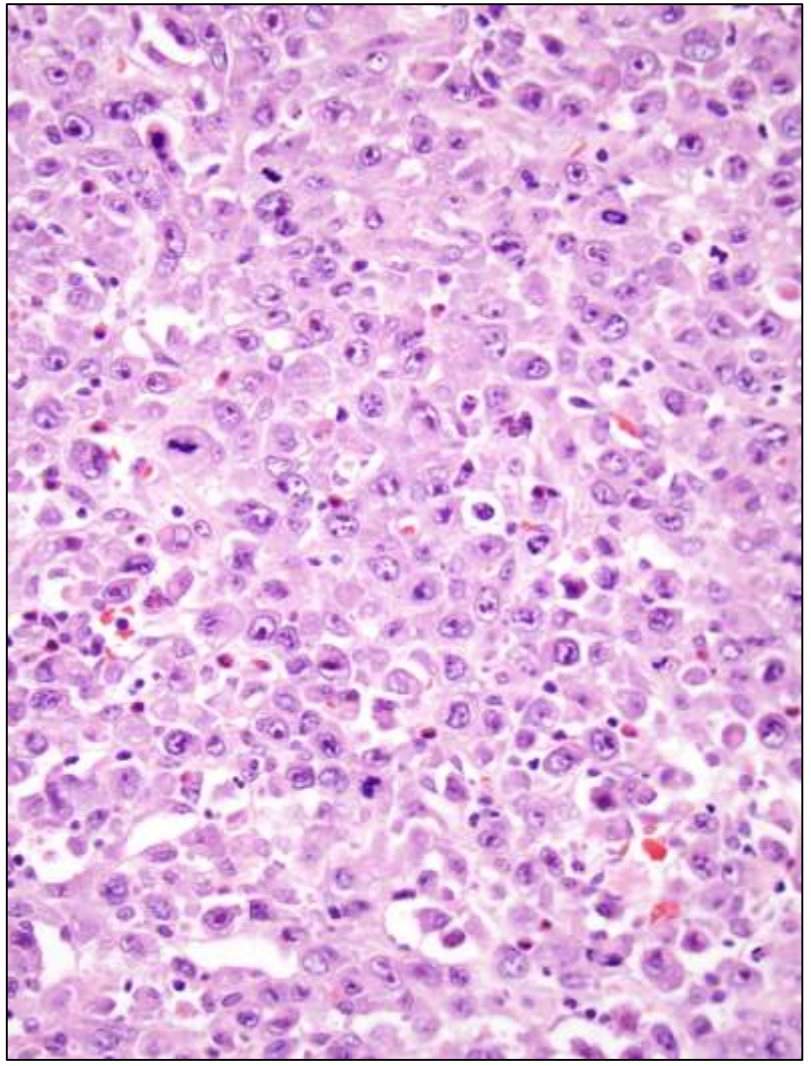


Anaplastic Large Cell Lymphoma Update

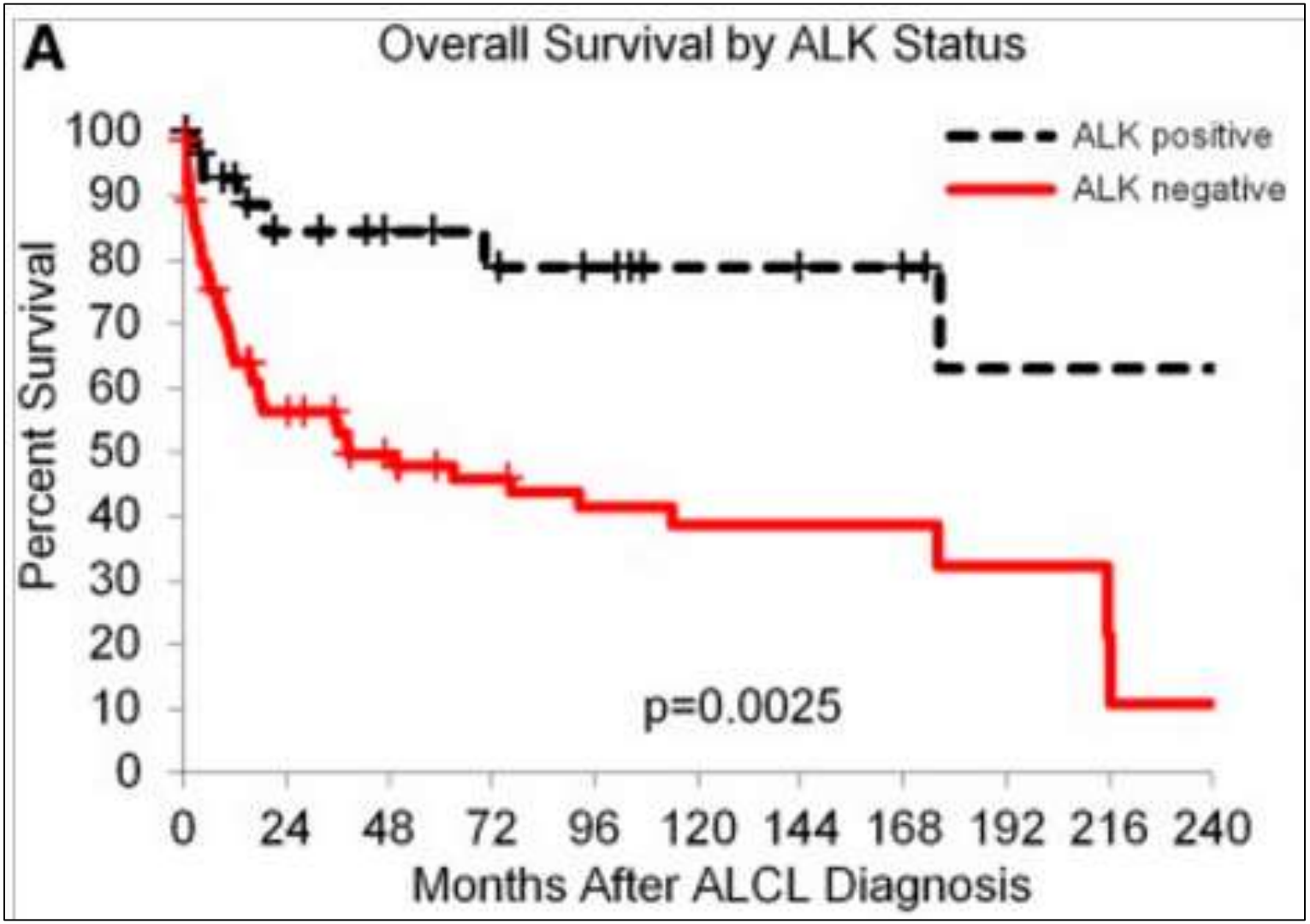
Dennis P. O'Malley, M.D.

Anaplastic Large Cell Lymphoma

- DEFINITION: A T cell lymphoma with expression of CD30, usually anaplastic morphology and variable clinical outcomes
- Formerly, there were “3” types of ALCL
  - Cutaneous ALCL – excellent prognosis; ALK negative
  - ALK-positive ALCL – good prognosis; translocation of *ALK* gene and overexpression of ALK protein
  - ALK-negative ALCL – poor prognosis (but mixed); ALK negative



SURVIVAL IN SYSTEMIC ALCL



Anaplastic large cell lymphoma

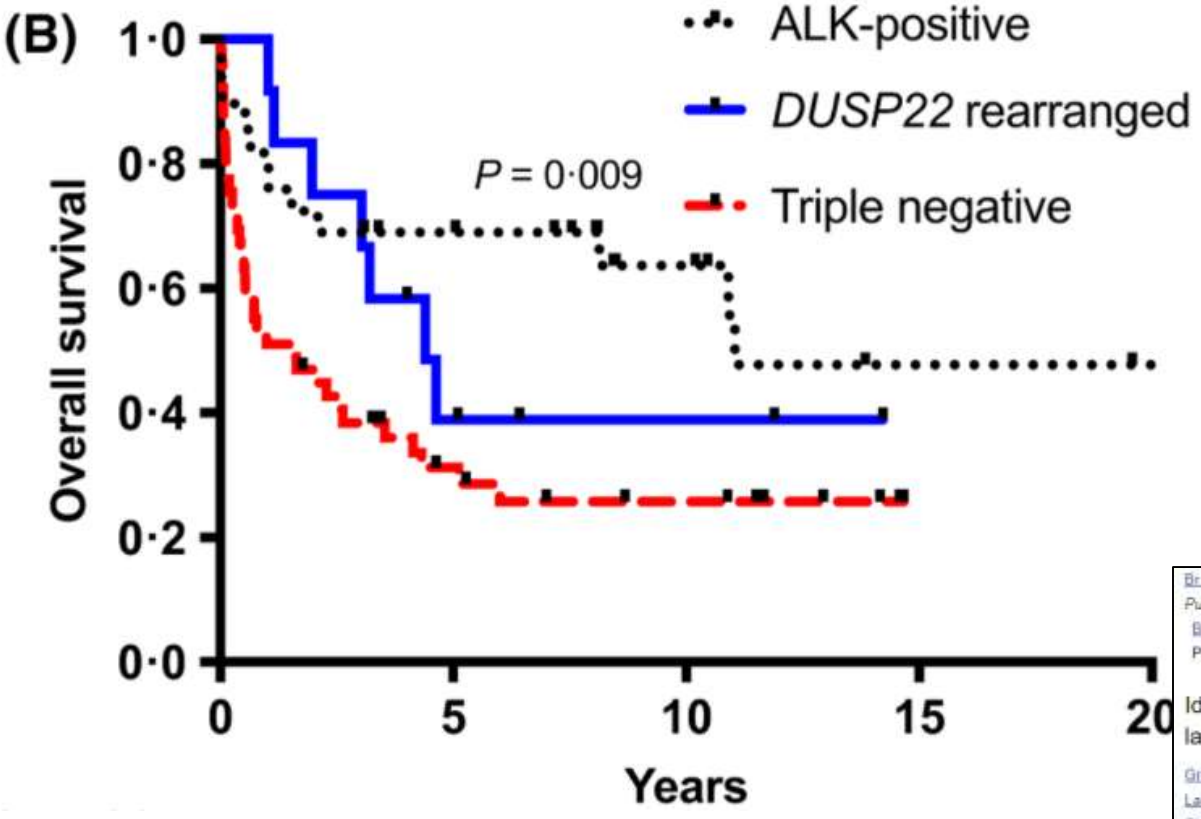
NOW:

- Cutaneous ALCL: unchanged
- Systemic ALK+ ALCL: unchanged

(below are all ALK-)

- S-ALCL with *DUSP22/IRF4* rearrangements
- S-ALCL with *TP63* rearrangements
- S-ALCL without *ALK, DUSP22* or *TP63 (triple negative)*
- Breast implant-associated ALCL*

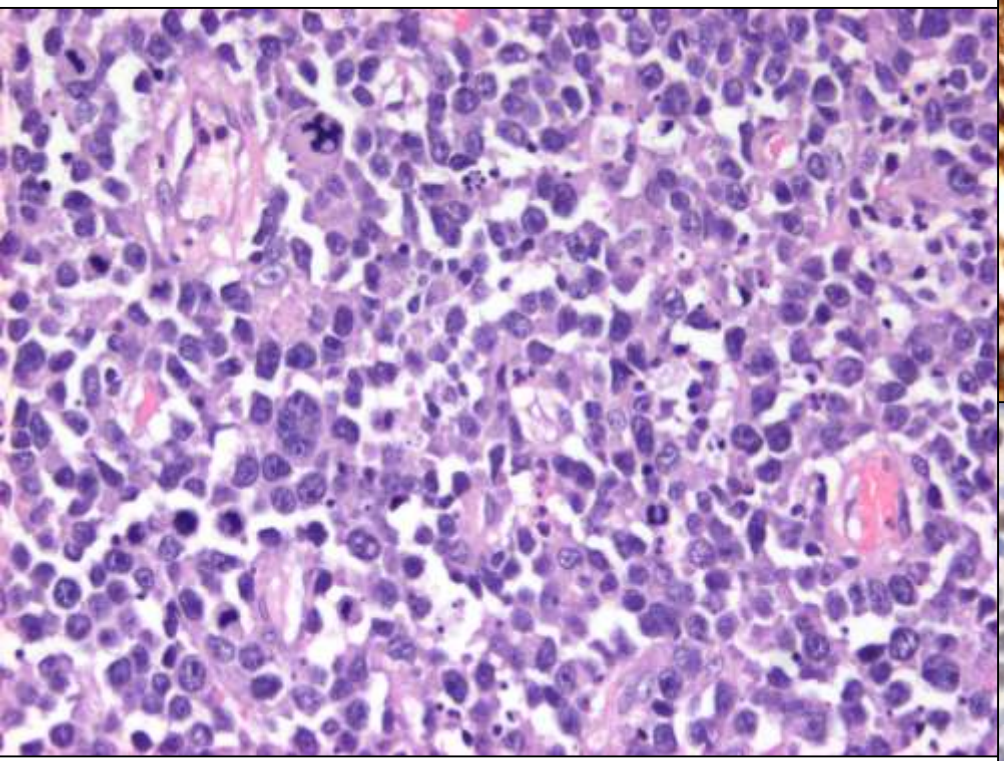
- ALCL, ALK+: good prognosis
- ALCL, *DUSP22/IRF4*: intermediate/poor prognosis
- ALCL, triple negative: very poor prognosis
- ALCL, *TP63*: very poor prognosis

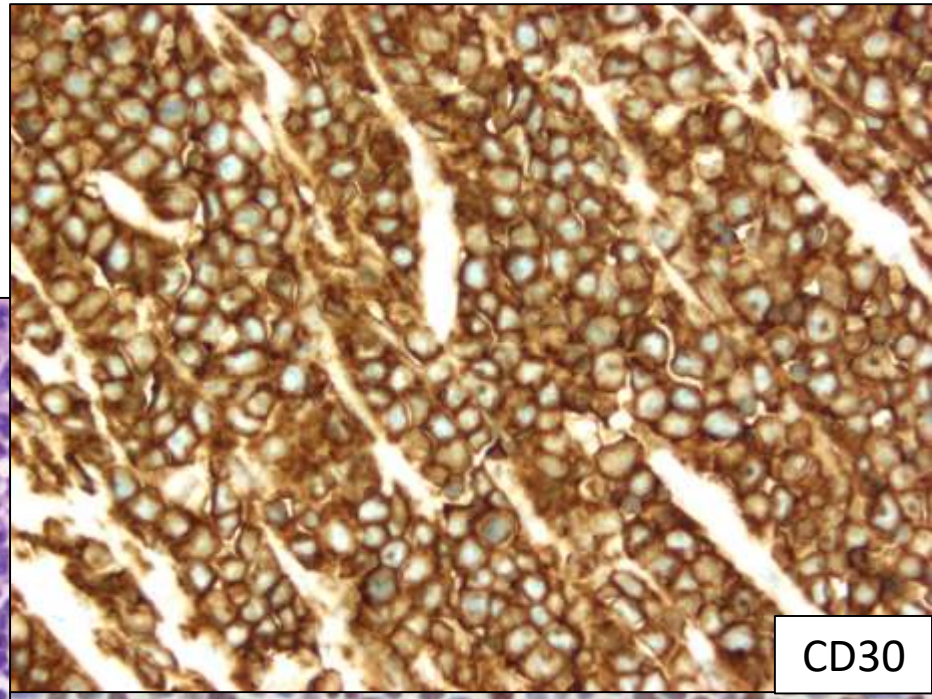


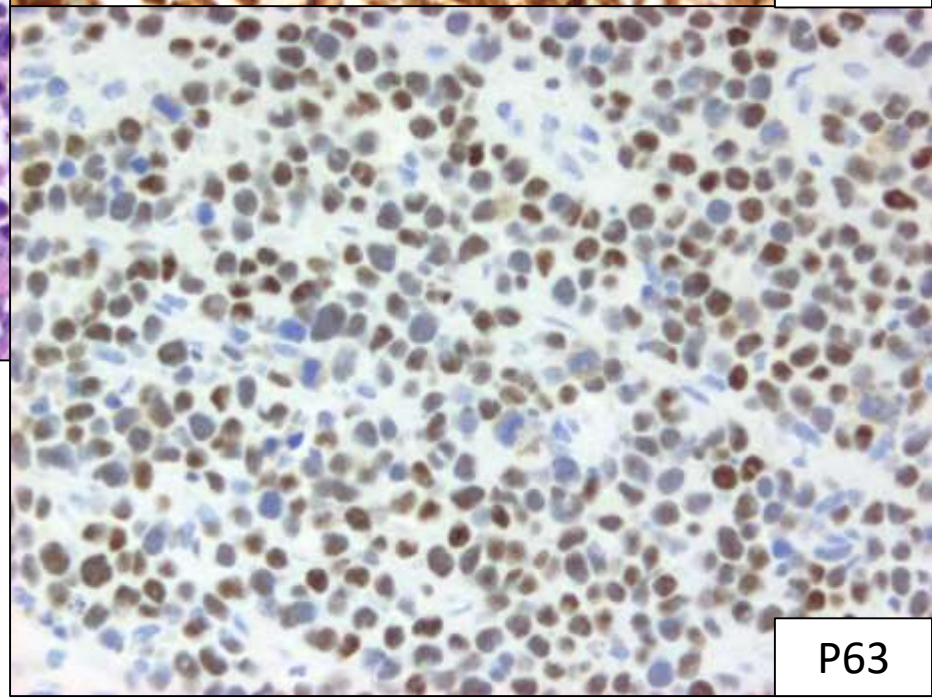
Br J Haematol. Author manuscript; available in PMC 2020 Nov 20.
Published in final edited form as:
Br J Haematol. 2019 Aug; 186(3): e28–e31.
Published online 2019 Mar 14. doi: 10.1111/bjh.15860
PMCID: PMC76
NIHMSID: NIHMS16
PMID: 308

Identification of high-risk *DUSP22*-rearranged ALK-negative anaplastic large cell lymphoma

Greg Hapgood,[1] Susana Ben-Neriah,[2] Anja Mottok,[2] Derrick G. Lee,[3] Kridel Robert,[2,4] Diego Villa,[1] Laurie H. Sehn,[1] Joseph M. Connors,[1] Randy D. Gascoyne,[5] Andrew L. Feldman,[6] Pedro Farinha,[5] Christian Steidl,[2] David W. Scott,[1] Graham W. Slack,[5] and Kerry J. Savage[1]

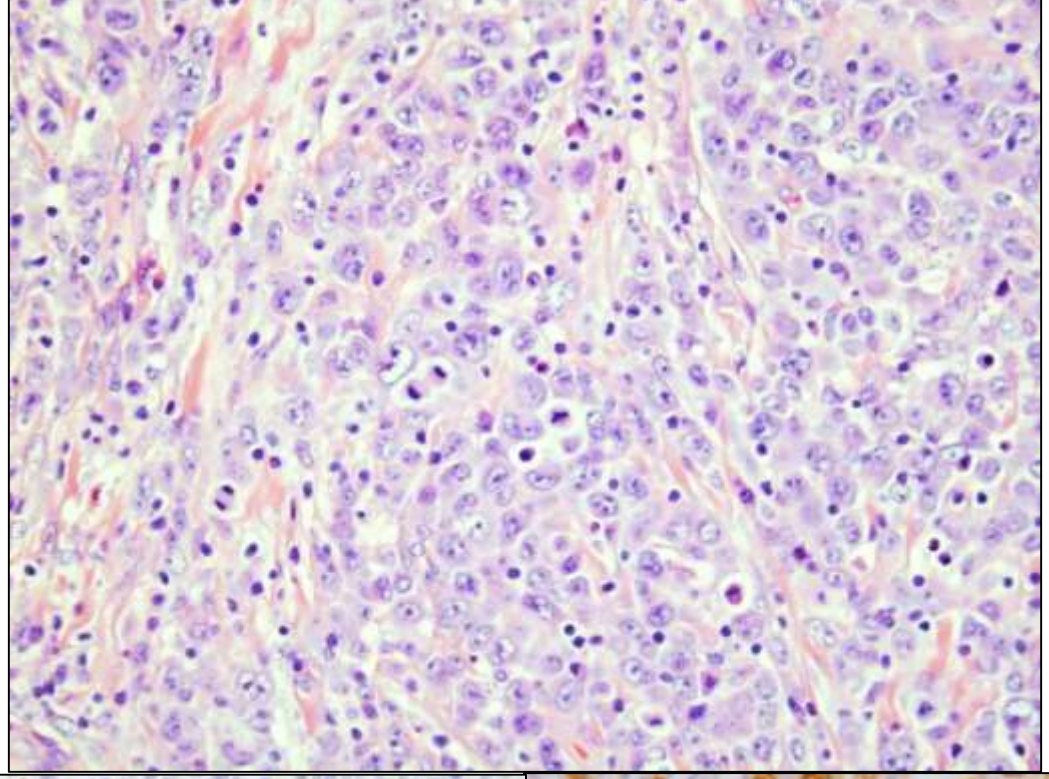


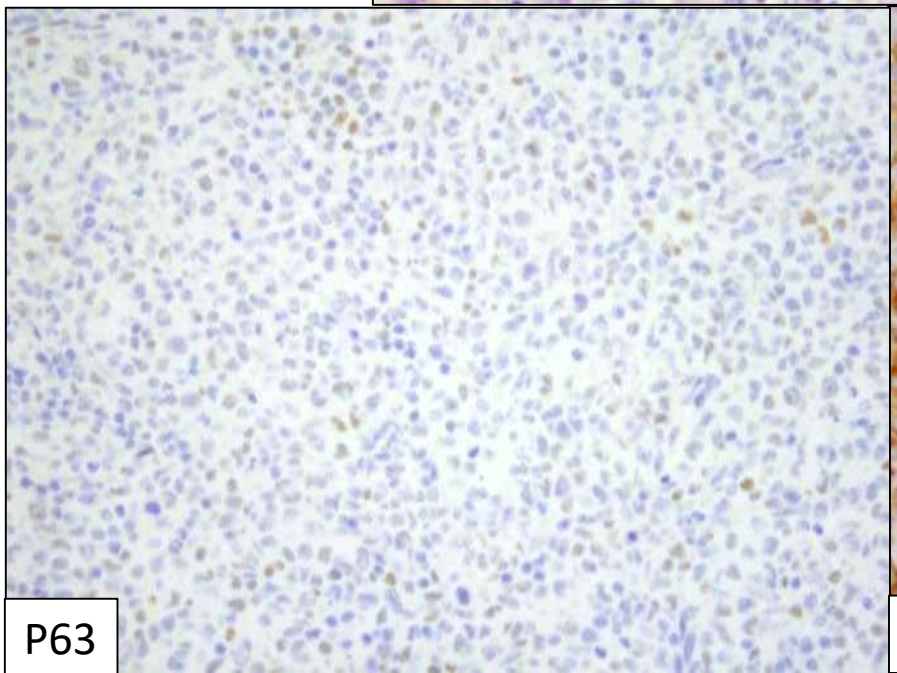


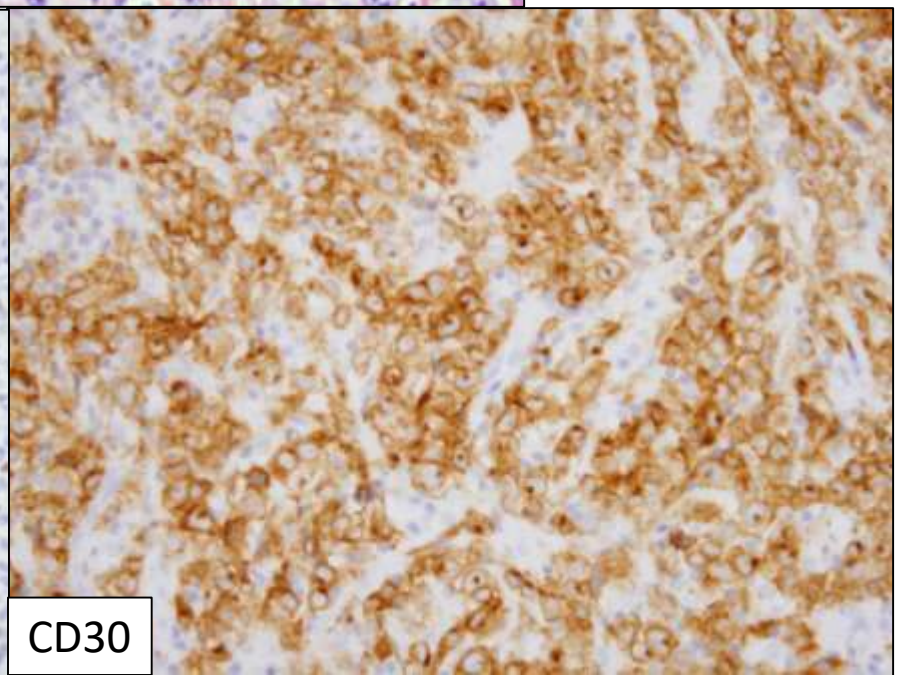


Small intestine – ALCL

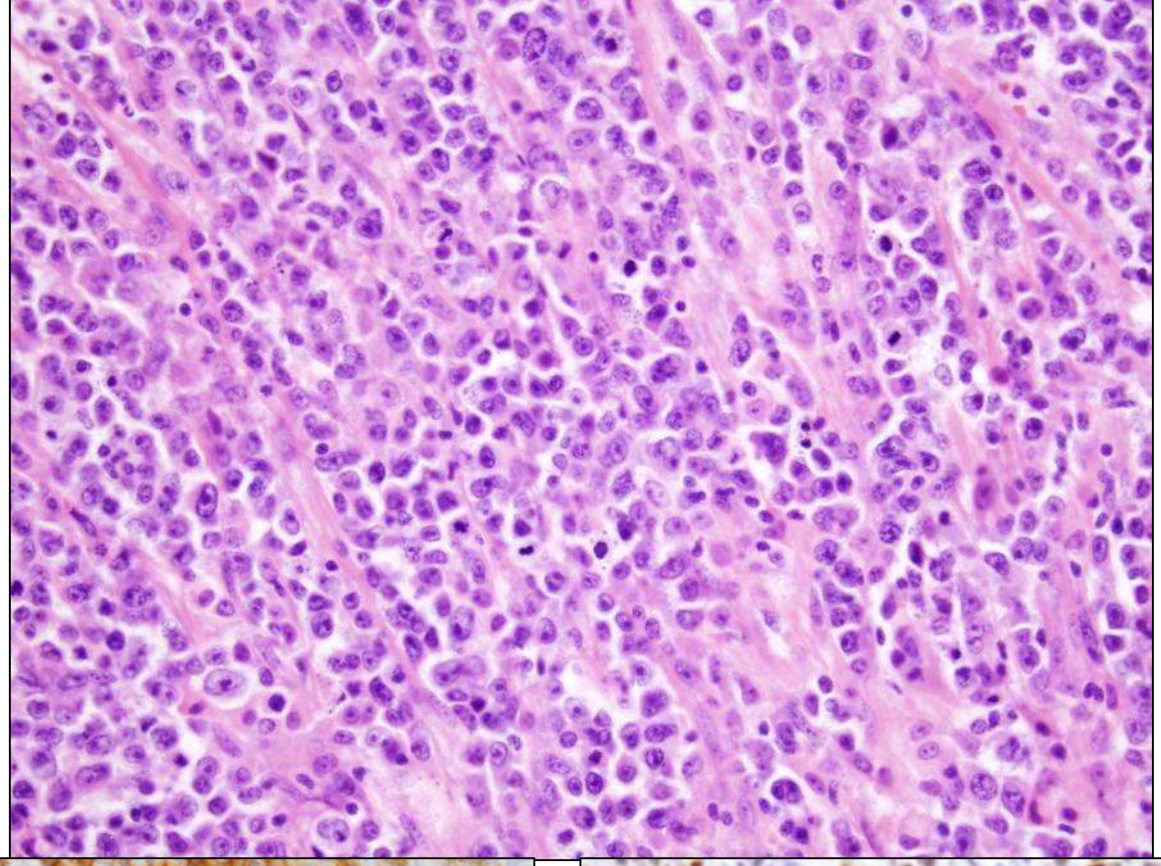
ALK-ALCL

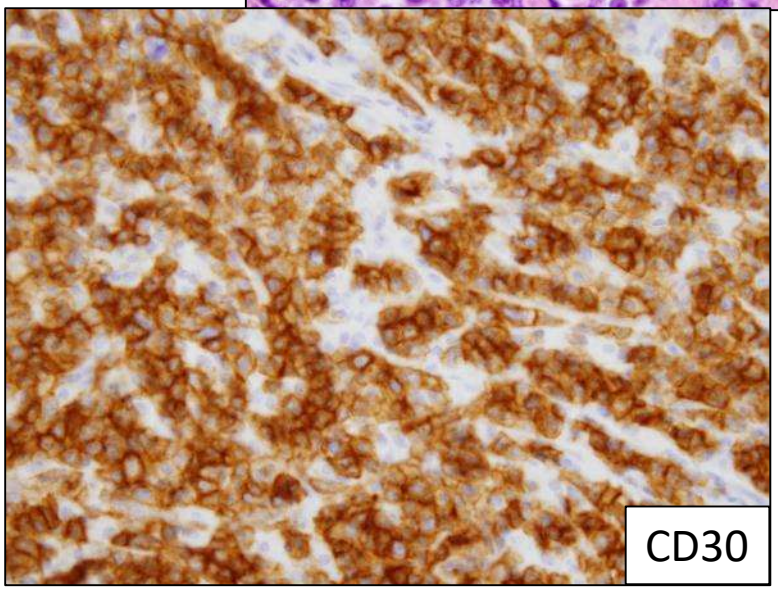


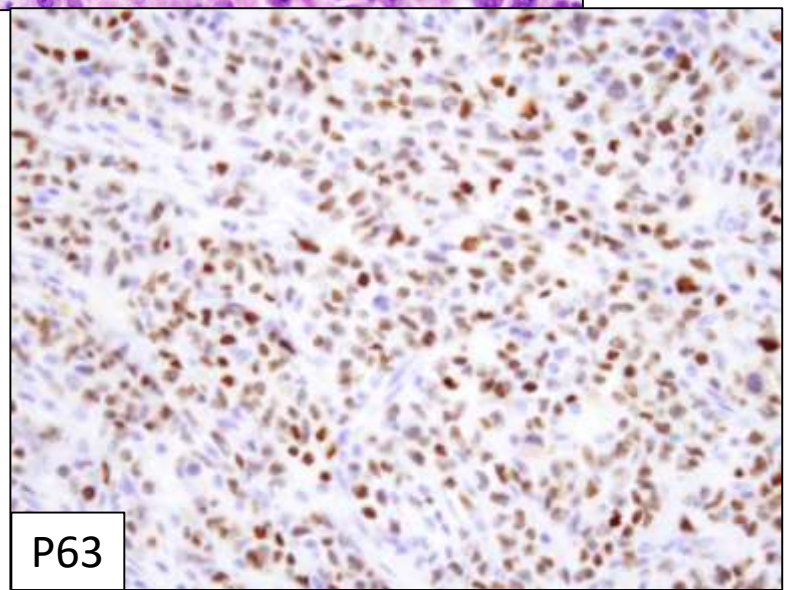




ALCL
ALK-

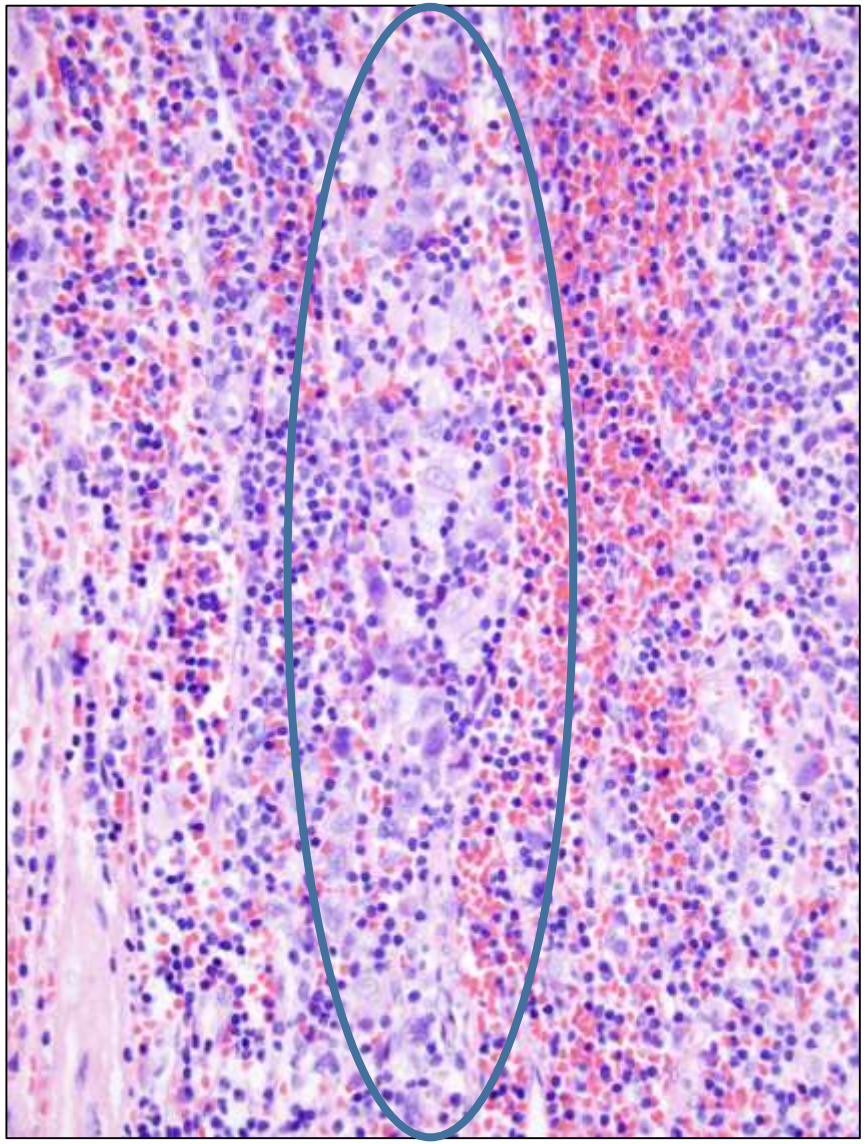






A few histologic ideas about ALCL

- Usually moderate-severe pleomorphism with large cell size
- Variable amounts of cytoplasm (usually pink)
- Highly variable background
- May attract eosinophils and less commonly neutrophils
- May have a sinusoidal distribution
- May have hallmark and donut cells
- *May break all these rules*



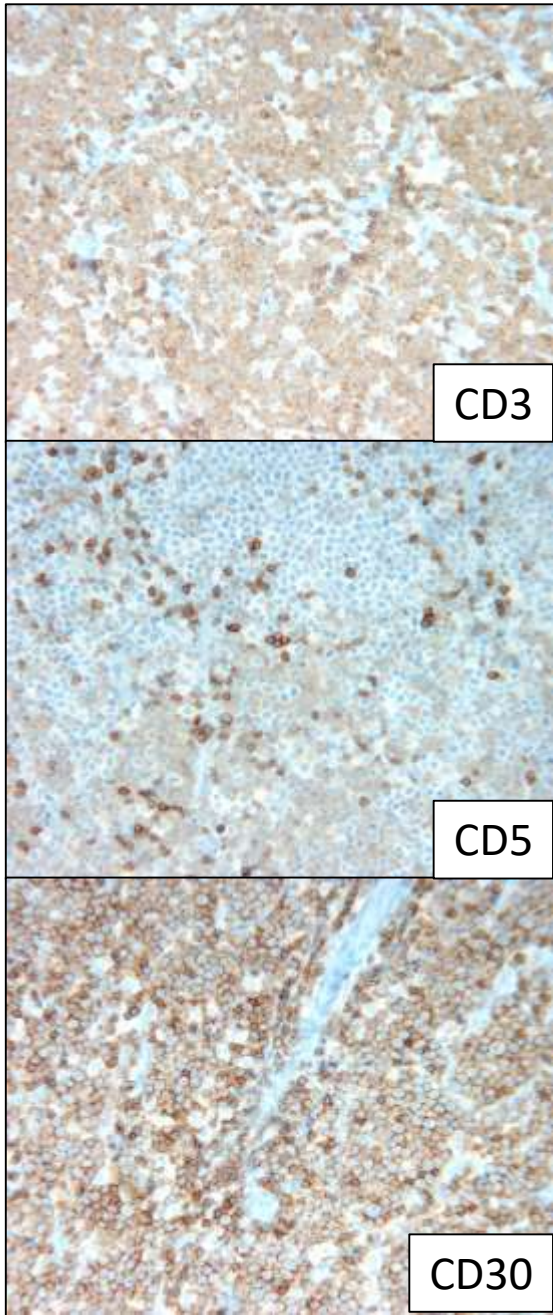
Practical pathology assessment of ALCL

- Identify T cell lymphoma with CD30 expression (in >75% of cells, strong)
- Location/clinical:
  - Is it skin? Breast capsule?
  - Is it lymph node? Extranodal?
- If ALCL, evaluate ALK by IHC
  - If ALK+, done. S-ALCL, ALK positive
- If ALK-, (e.g. S-ALCL, ALK negative)
  - FISH for *DUSP22* (positive, intermediate/poor prognosis)
  - *FISH *TP63* (positive, POOR prognosis)
  - If negative for all, then “triple negative” (poor prognosis)

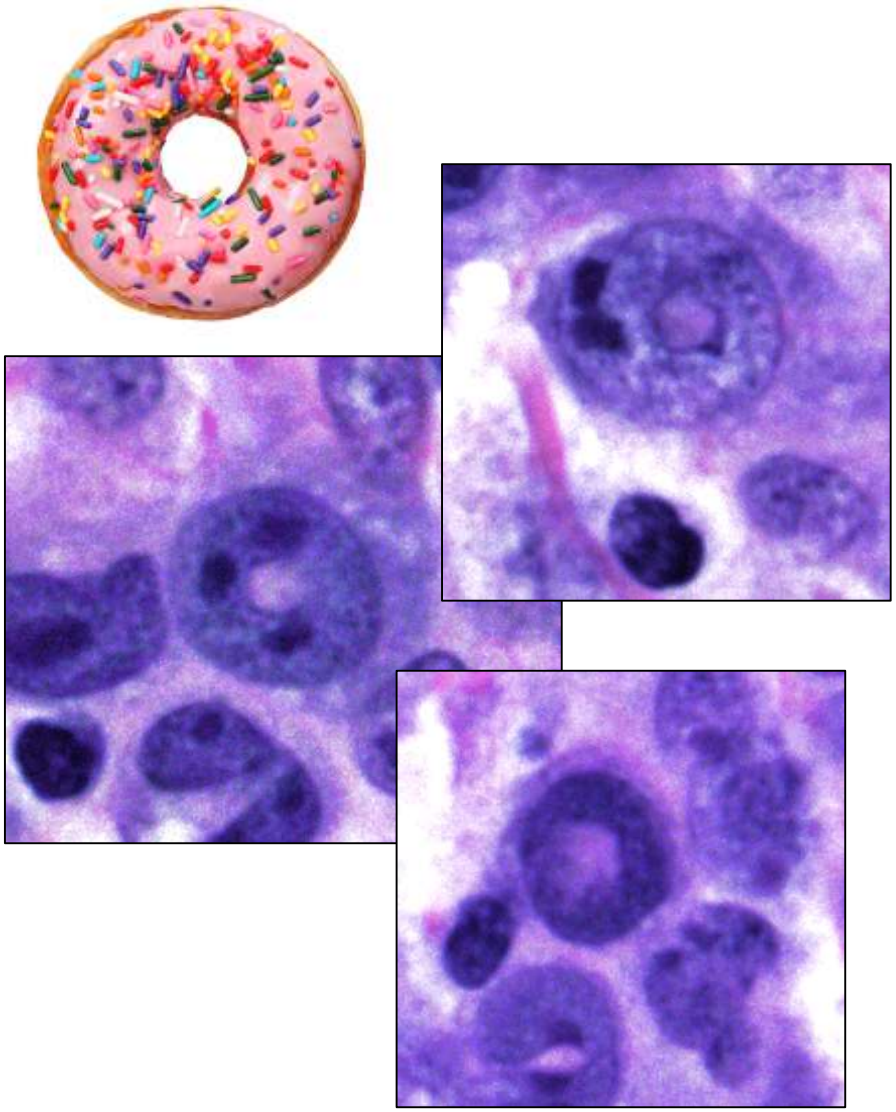
*Can screen for TP63 by performing IHC

IHC assessment of ALCL

- CD3 (absent 50%), CD45 (absent 50%), CD5 (absent 50%)
- CD30 expressed strongly in at least 75% (or consider CD30+ PTCL)
- Pan T cell antigens I use: CD2, CD43
- Perform ALK1, P63
- Perform cytotoxic markers
- “Null” type (I’m not a big believer)
- Things I rely on less: CD4, CD8, MUM1 (expressed in all cases), CD7, TCR beta/delta (usually negative)



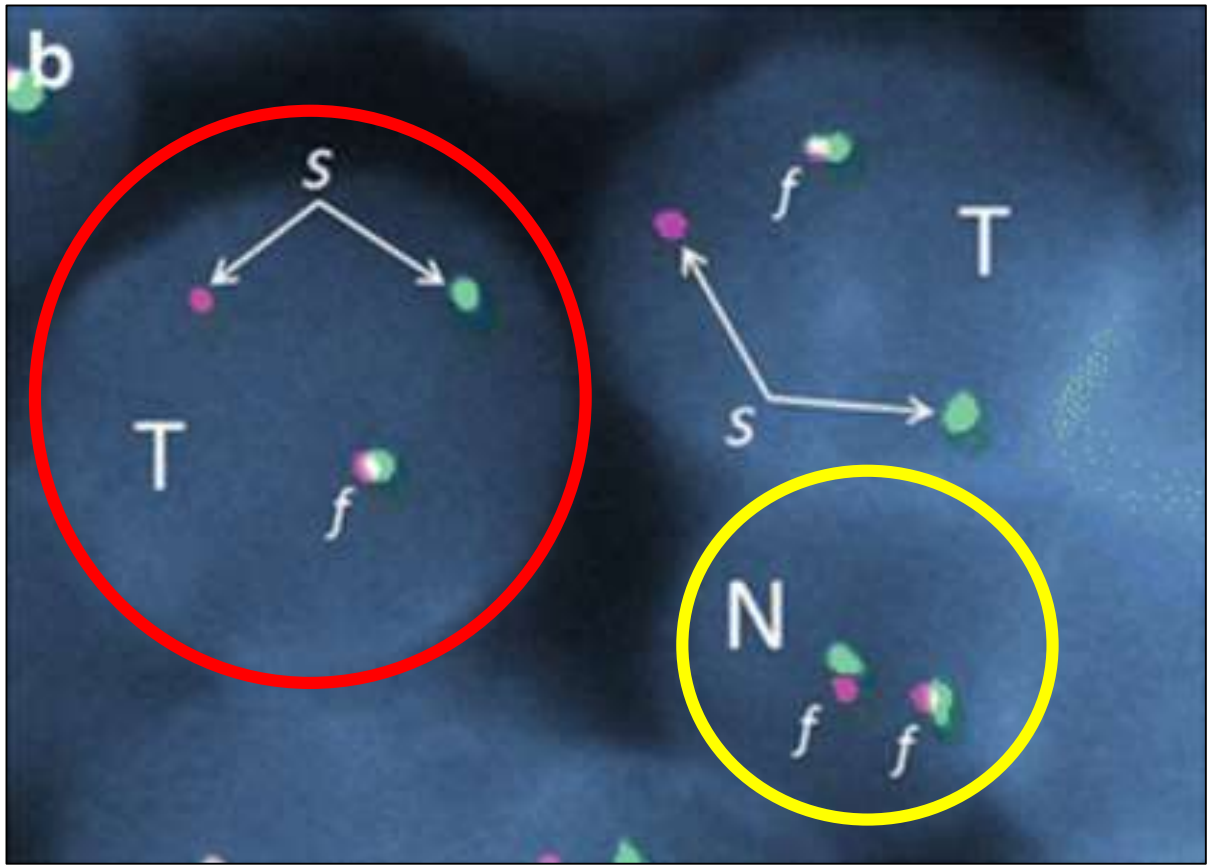
DUSP22 rearrangement in ALCL



Some differences

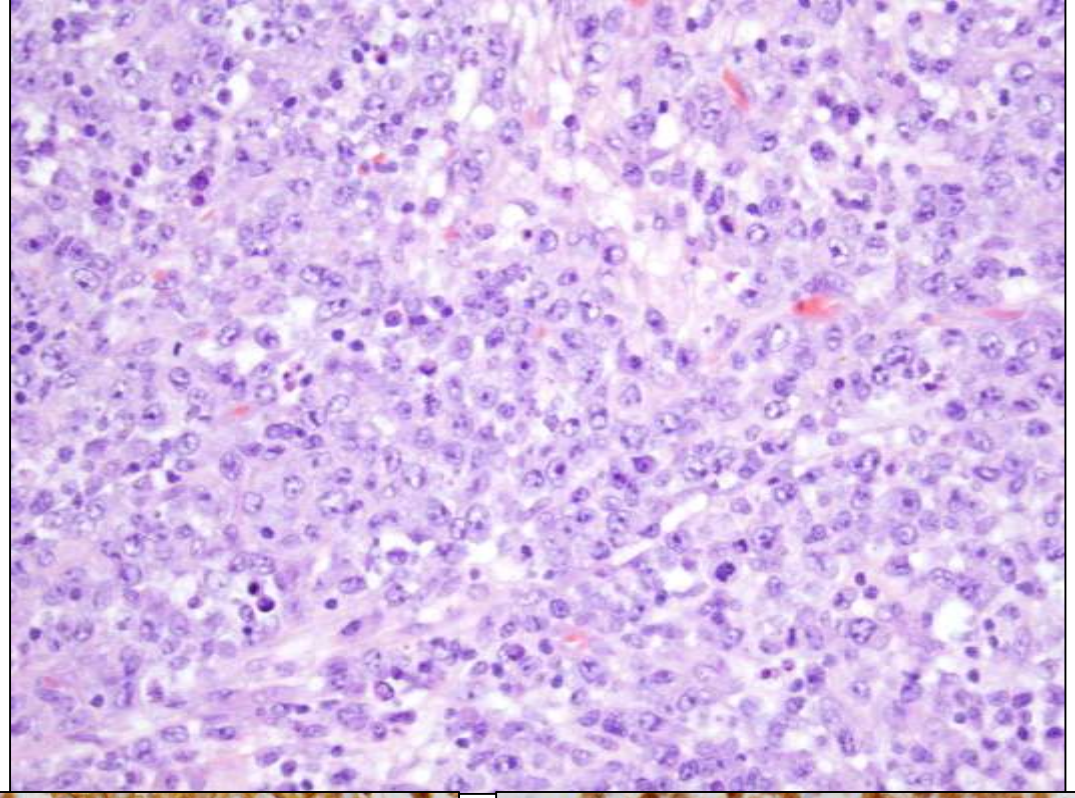
- Cytotoxic marker negative
- Negative PD-L1
- Strong MUM1
- LEF1 loss
- Some PAX5 positive
- Donut cells

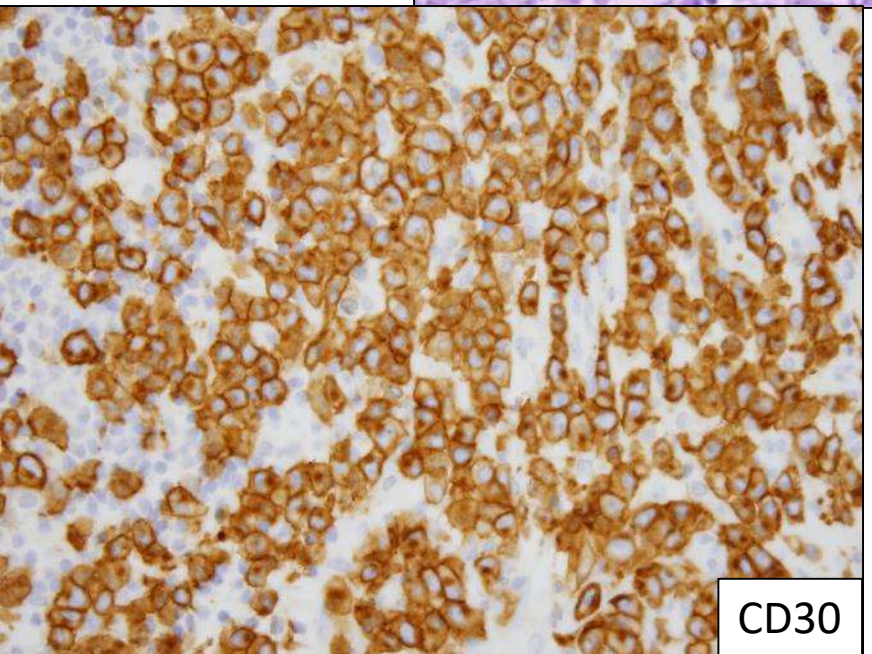
DUSP22 FISH in ALCL

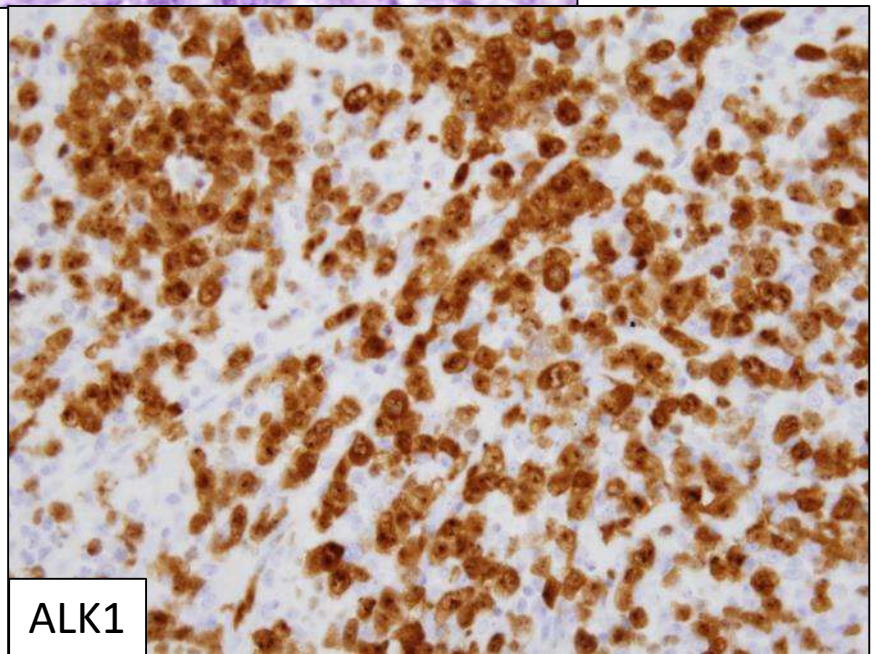


DUSP22: break-apart probe

ALK+ ALCL

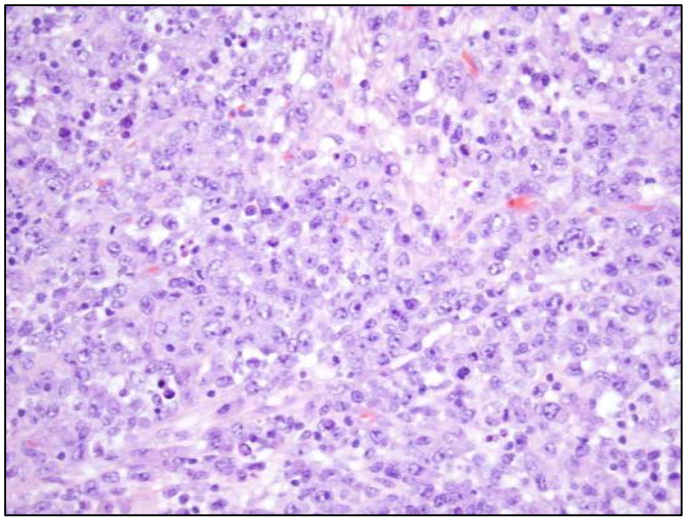


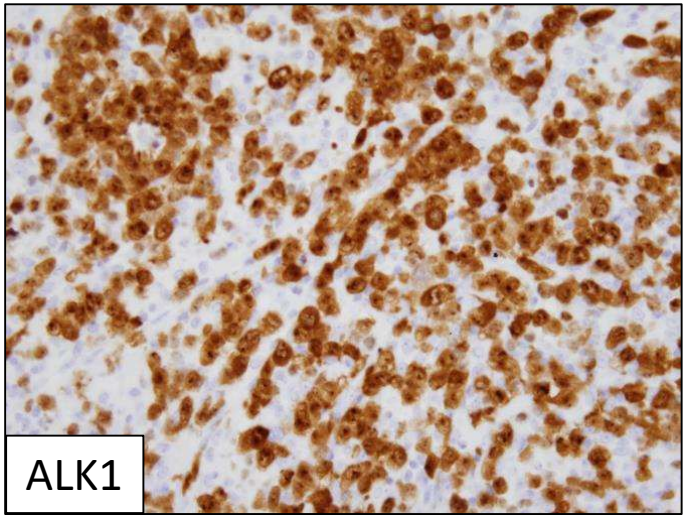




Genetics in ALCL, ALK positive

- *t(2;5) NPM1-ALK* fusion transcripts (nuclear + cytoplasmic ALK expression)
- Present in approximately 75–85% of ALK-positive ALCL
- More than 20 other *ALK* partners
- *ALK* partner gene (*NPM1* or other) does not appear to be a significant prognostic factor





Many different *ALK* fusion partners have been identified

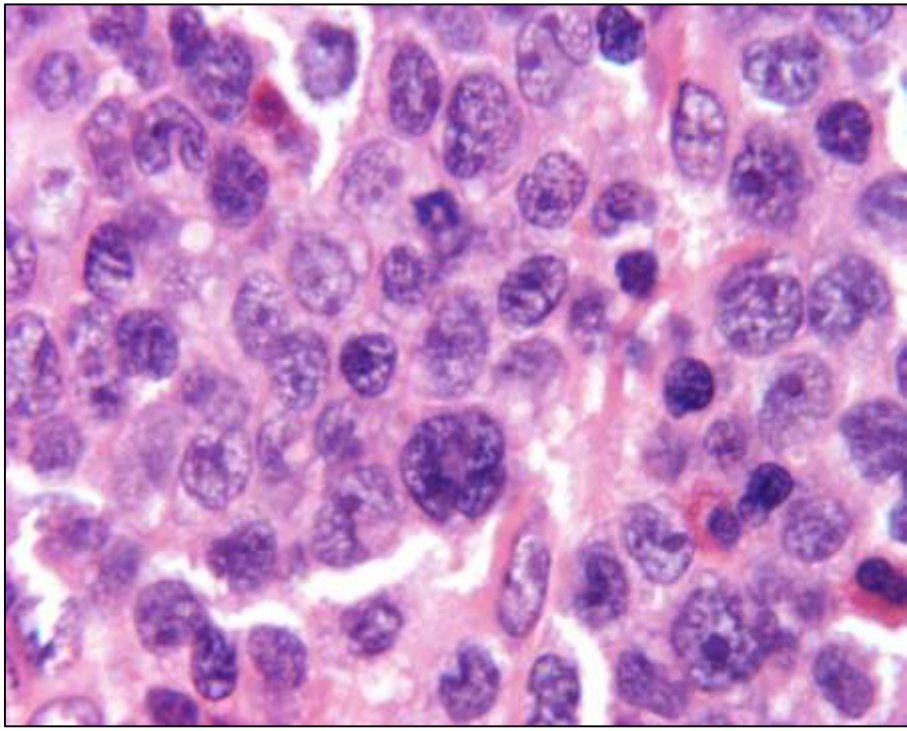
Fusion partner	Tumor types
ATIC	ALCL and IMT
CARS	IMT
CLTC	ALCL, DLBCL, IMT
DCTN1	IMT
EML4	Lung AdCA, IMT
FN1	IMT
KIF5B	Lung AdCA
KLC1	Lung AdCA
LMNA	IMT
MSN	ALCL
MYH9	ALCL

Fusion partner	Tumor types
NPM	ALCL
PPFIBP1	IMT
PRKAR1A	IMT
RANBP2	EIMS
RRBP1	EIMS
SEC31A	IMT
SQSTM1	DLBCL, EFH
TFG	ALCL, IMT, Lung AdCA
TPM3	ALCL, IMT
TPM4	IMT
VCL	EFH, RCC

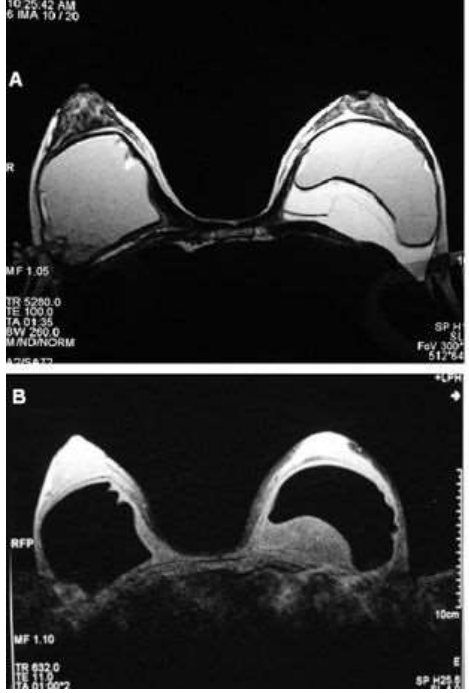
Courtesy Jason Hornick

Systemic ALCL - summary

- At least 4 different genetic types
- Evaluation of all prognostic types recommended
- Combination of IHC and FISH
  - ALK1 IHC, P63 IHC (+/-), *TP63* FISH, *DUSP22* FISH



Breast implant associated ALCL*



1895
First attempts for breast augmentation by Vincenz Czerny

1900s
Development of injectable substances for breast augmentation

1962
First-generation silicone implants

1964
First saline-filled implants

1970s
Second-generation implants

1980s
Third-generation implants

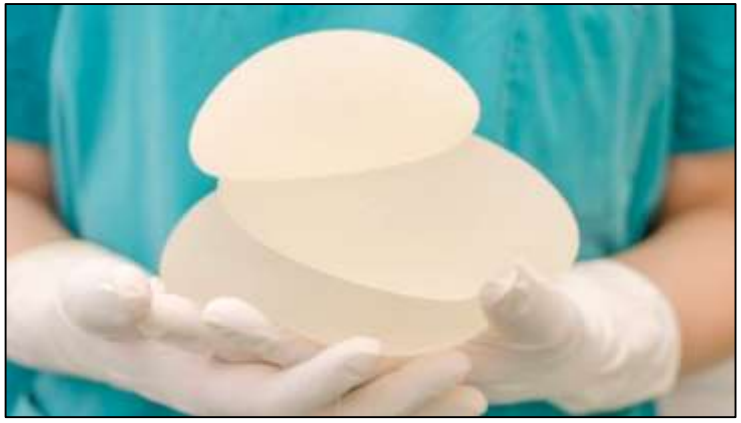
1992
U.S. Food and Drug Administration moratorium on the use of silicone implants

1992
Fourth-generation implants

1993
Fifth-generation implants

2006
End of the FDA moratorium

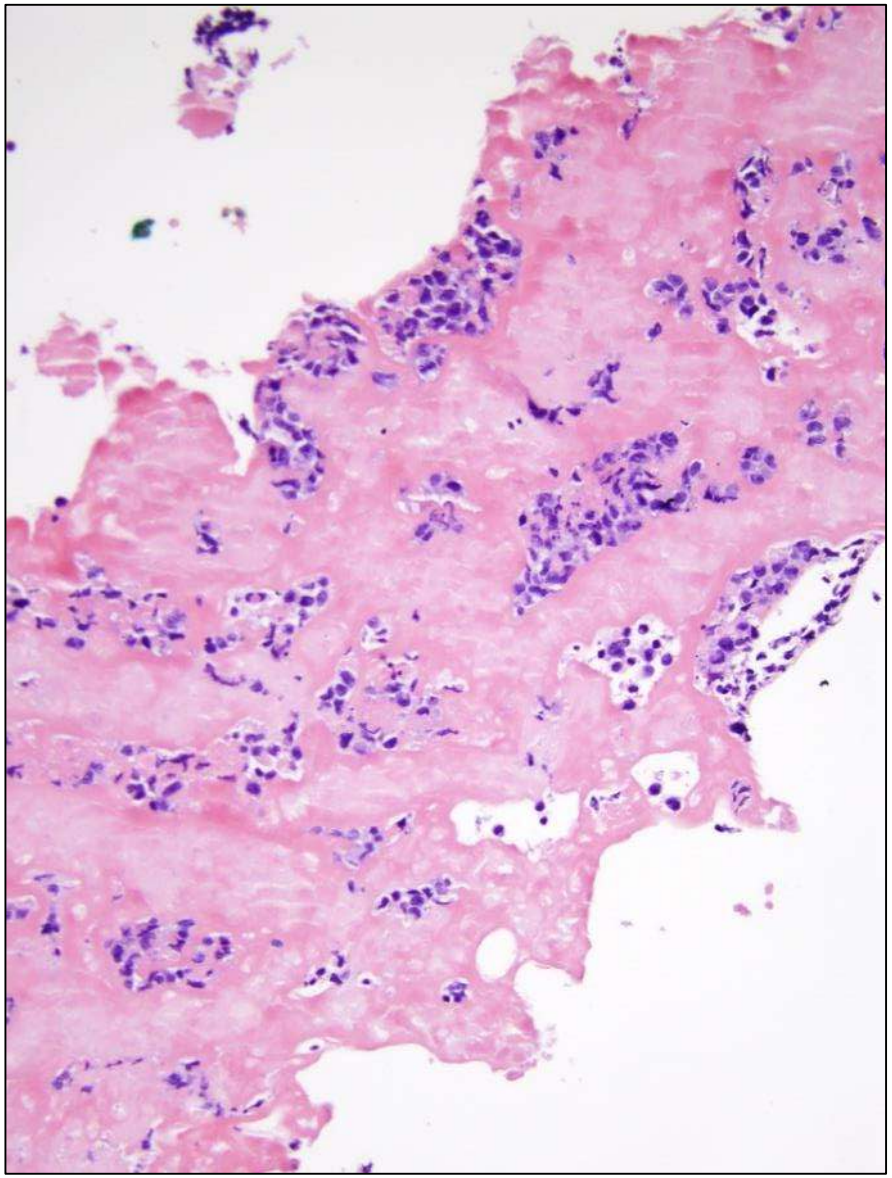
TODAY

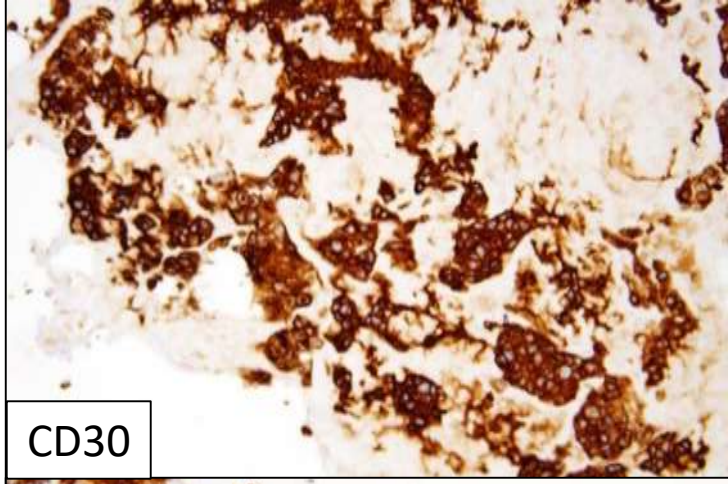


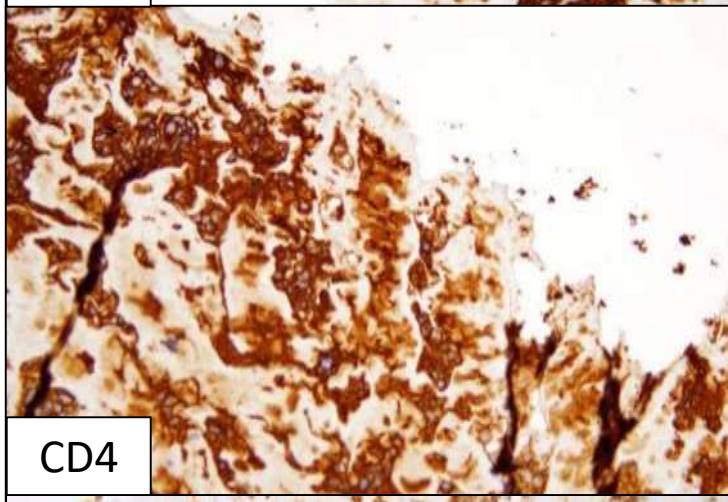
Breast implant-associated ALCL

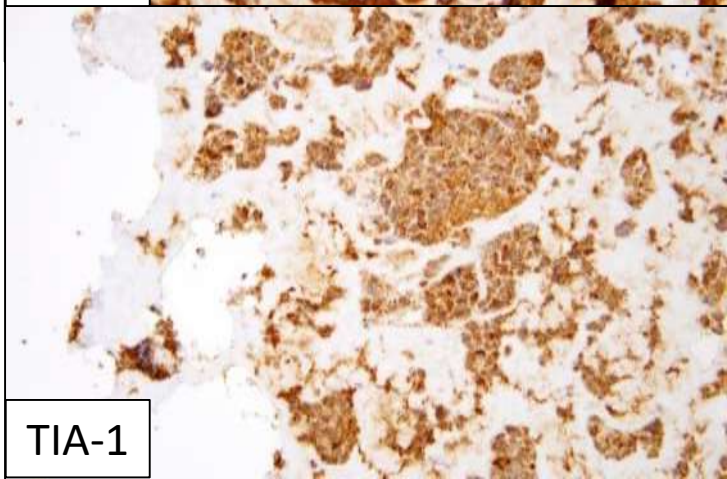
- Presents as an accumulation of seroma fluid between implant and surrounding fibrous capsule
- Both saline and silicone-filled implants have been implicated
- Almost all are textured implants
- Median interval from implant to lymphoma of 10 years
- In most cases, the neoplastic cells are confined to the seroma fluid, without invasion of the capsule
- Conservative management will suffice in most cases
- In some cases, there is invasion through the capsule
- Risk of lymph node involvement and systemic spread, warranting systemic chemotherapy

Breast implant associated ALCL*









Best Practices Guideline for the Pathologic Diagnosis of Breast Implant–Associated Anaplastic Large-Cell Lymphoma

Elaine S. Jaffe, MD[1]; Binita S. Ashar, MD, MBA[2]; Mark W. Clemens, MD[3]; Andrew L. Feldman, MD[4]; Philippe Gaulard, MD, PhD[5]; Roberto N. Miranda, MD[6]; Aliyah R. Sohani, MD[7]; Timothy Stenzel, MD, PhD[8]; and Sung W. Yoon, MD[2]

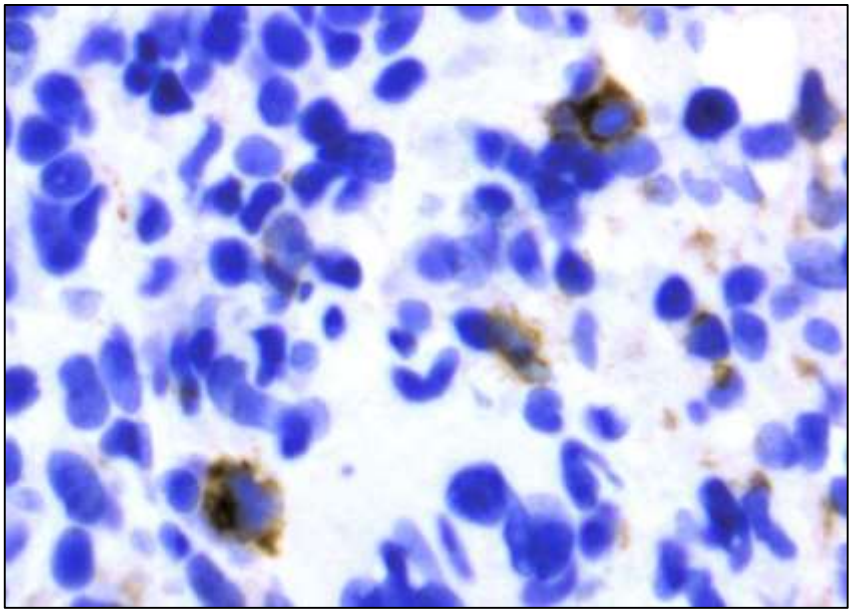
TABLE 1. Staining Panel for Evaluation of Cell Blocks and Capsulectomy Specimens

Stain(s)	Rationale
CD30	Strongly and uniformly positive, by definition, in BIA-ALCL
ALK1	If negative, excludes systemic ALK-positive ALCL
EMA	Variably positive in BIA-ALCL
CD4, CD43[a]	More commonly preserved among pan-T-cell antigens
CD2, CD3, CD5, CD7[a]	More commonly diminished or lost among pan-T-cell antigens
TIA-1, granzyme B, Perforin[a]	Cytotoxic granule proteins frequently positive in BIA-ALCL
CD68 or CD163	Positive in histiocytes; distinguish histiocytes from lymphoma cells
Pan-keratin	Excludes carcinoma, particularly in patients with EMA-positive disease or patients with a history of breast cancer
CD20	Excludes DLBCL
PAX5	Excludes DLBCL and CHL
CD138	Excludes PBL and PEL
HHV-8 LANA	Excludes PEL
EBER ISH[b]	Excludes neoplasms with EBV coinfection, including EBV-positive DLBCL, fibrin-associated large B-cell lymphoma, CHL, and PBL
S-100 or Melan-A	Excludes metastatic melanoma
CD31, CD34 or ERG	Excludes angiosarcoma, particularly in patients with prior radiation therapy for breast cancer

JCO, 2020

IHC evaluation of BIA-ALCL

- CD30 is first priority
- Careful: plasma cells can express CD30!
- CD79a is useful for plasma cells and possible ringer (see later)



CD30: BM plasma cells

1st Case

- Keech and Creech. 1997. Patient with saline implant

(more later)

- 518 cases American Society of Plastic Surgeons Patient registry from 25 countries 1-3/1,000,000
- Virtually all in textured implants
- Proposed contributing factors
  - Bacterial component, implant surface texture, genetic factors, mechanical friction

Current Challenges in Breast Implantation

Zuzanna Pelc †, Magdalena Skórzewska †, Andrzej Kurylcio, Paweł Olko, Joanna Dryka, Piotr Machowiec, Marcela Maksymowicz, Karol Rawicz-Pruszyński * and Wojciech Polkowski

Gluteal Implant-Associated Anaplastic Large Cell Lymphoma

José Mendes, Jr., M.D.
Vinicius A. Mendes
Maykeh, M.D.
Luiz Fernando Frascino, M.D., Ph.D.
Flavia F. S. Zacchi, M.D.
São Paulo, Brazil

Summary: The association of anaplastic large cell lymphoma (ALCL) to breast implants (breast implant-associated ALCL) has brought back the discussion on the clinical safety of the use of silicone implants. A 63-year-old woman came to our institution in early 2015, reporting a gluteal augmentation with silicone implants in 2006 and a recent increasing volume and distortion of the left buttock. Radiologic imaging showed a large amount of fluid collection around the implant. The left side implant was removed and the capsule was left intact, presupposing a future reimplantation. The fluid collected was positive for *Staphylococcus aureus*. Three years later, she presented again with a new seroma on the explanted side and was submitted to total capsulectomy and fluid drainage, and the material was submitted to laboratory examination. Culture results were negative. Pathologic preparation and sections of the capsule and lumps showed large cells characterized by horseshoe-shaped nuclei. Immunohistochemistry was positive for CD30/CD4 and negative for anaplastic lymphoma kinase, confirming the presence of ALCL, then associated with gluteal implant, an event not described in literature. Positron emission tomography/computed tomography and bone marrow biopsy were performed, and neither showed any other sites involved. The same disease in a new location introduces important discussions about the understanding of this abnormality and poses certain risks and safety issues to clinical scenarios to be discussed. Regardless of whether it is a breast implant-associated ALCL or a gluteal implant-associated ALCL, now we are probably facing an implant augmentation–associated disease and a new international alert should be addressed to the scientific community. (*Plast. Reconstr. Surg.* 144: 610, 2019.)

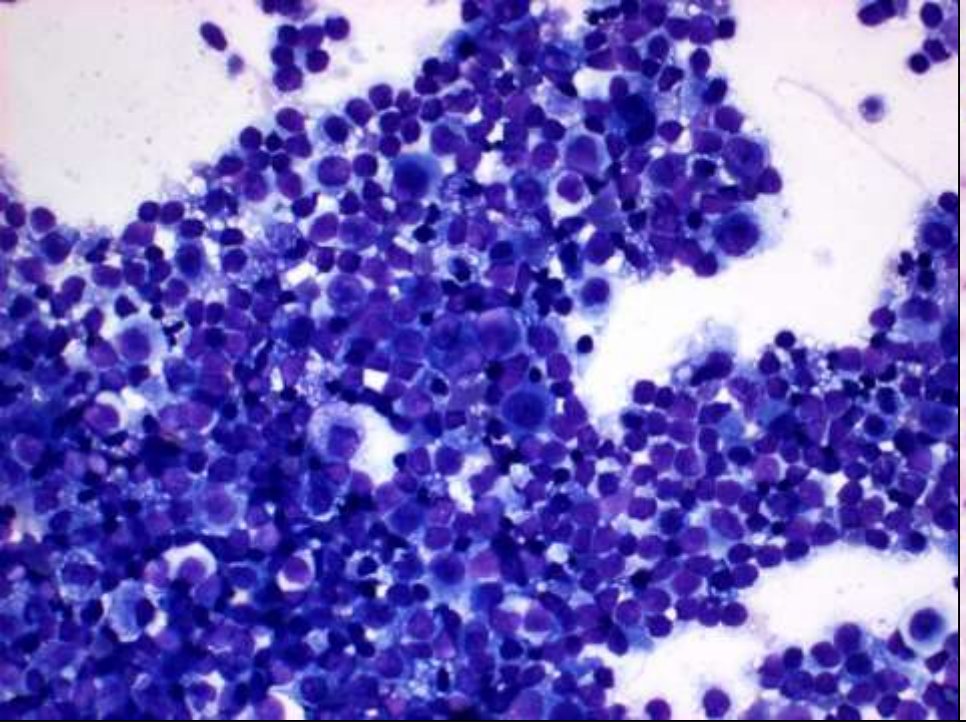
CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, V.

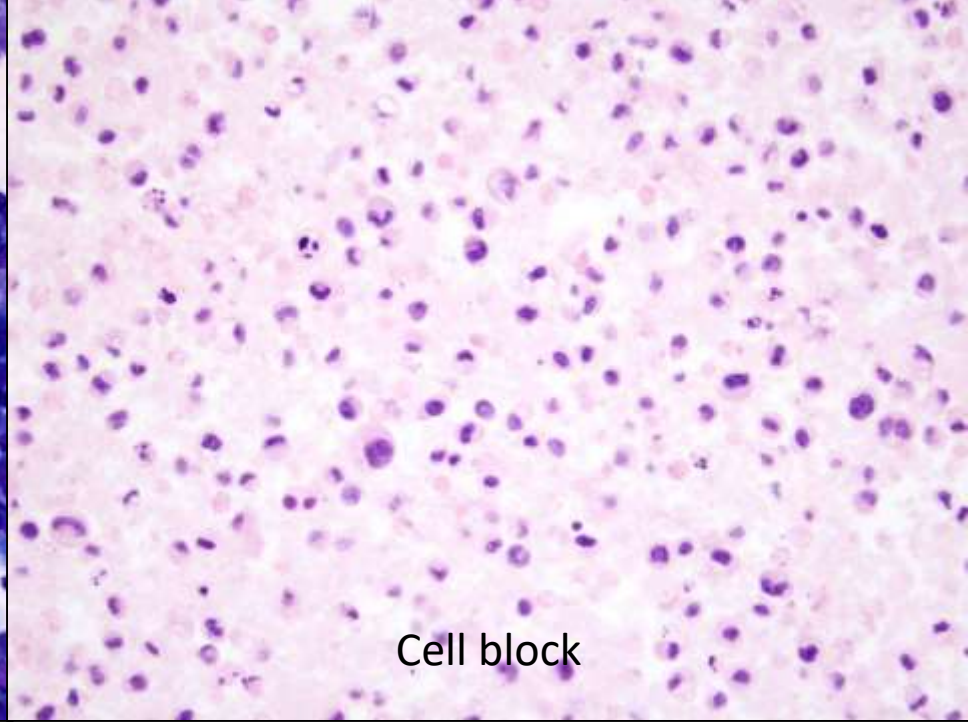
BIA-ALCL: A practical comment

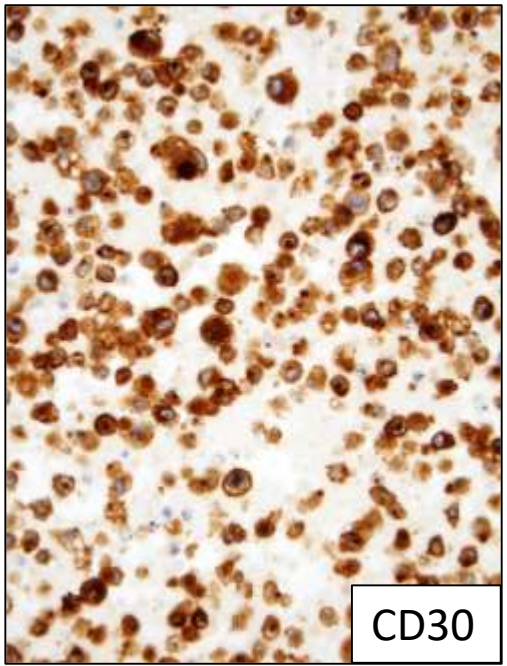
- Essentially **ALL** BIA-ALCL cases will be associated with a medicolegal case
  - Ask yourself if you want to be called in a medicolegal case even if you have done nothing wrong
- As such:
  - Sample thoroughly
  - Stain lots
  - Consider sending consult to an expert (if in doubt, send it out!)

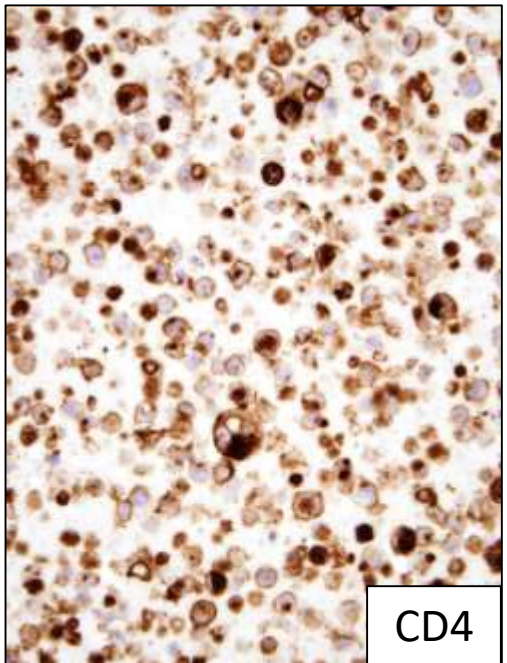
Evaluation of implant associated serous fluid

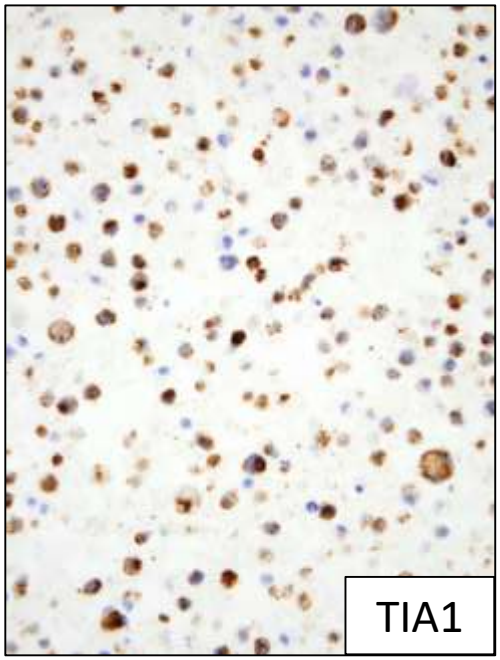
- Cytology should be done on cytospin samples
- It is not sensitive, but may be diagnostic
- Flow cytometry of serous fluid is not sensitive but may be specific
  - Caveat: this requires specialized gating and non-standard flow tubes to be performed (see medicolegal commentary)




Cell block


CD30


CD4


TIA1

Epstein–Barr-virus-positive large B-cell lymphoma associated with breast implants: an analysis of eight patients suggesting a possible pathogenetic relationship

Mod Path, 2021

L. Jeffrey Medeiros[1], Mario L. Marques-Piubelli[2], Valentina F. I. Sangiorgio[3], Roberto Ruiz-Cordero[4], Francisco Vega[1], Andrew L. Feldman[5], Jennifer R. Chapman[6], Mark W. Clemens[7], Kelly K. Hunt[8], Mark G. Evans[1], Christine Khoo[9], Stephen Lade[9], Mark Silberman[10], Jerzy Morkowski[11], Edward M. Pina[12], Daniel C. Mills[13], Christopher M. Bates[14], Winston B. Magno[15], Aliyah R. Sohani[16], Beth A. Sieling[17], Joseph M. O'Donoghue[18], Chris M. Bacon[19], Neill Patani[20], Despina Televantou[21], Suzanne D. Turner[22], Laura Johnson[23], Fiona MacNeill[24], Andrew C. Wotherspoon[25], Swaminathan P. Iyer[26], Luis E. Malpica[26], Keyur P. Patel[1], Jie Xu[1] and Roberto N. Miranda[1]✉

Breast implant-associated EBV-positive diffuse large B-cell lymphoma: Two case reports and literature review

Pathol Res Prac, 2021

Sarah Morgan[a], Rosemarie Tremblay-LeMay[a,b], Joan E. Lipa[d], Monalisa Sur[e], Jan Delabie[a,b], Kevin Imrie[f], Michael Crump[g], Laura J. Snell[d], Zeina Ghorab[a,c,*]

EBV$^+$ diffuse large B-cell lymphoma associated with chronic inflammation expands the spectrum of breast implant–related lymphomas

Blood, 2020.

Lénaïg Mescam,[1] Vincent Camus,[2,3] Jean-Marc Schiano,[4] José Adélaïde,[5] Jean-Michel Picquenot,[6] Arnaud Guille,[5] Marie Bannier,[7] Philippe Ruminy,[3] Pierre-Julien Viailly,[3] Fabrice Jardin,[2,3] Reda Bouabdallah,[4] Isabelle Brenot-Rossi,[8] Elodie Bohers,[3] Cyrielle Robe,[9] Camille Laurent,[10] Daniel Birnbaum,[5] Andrew Wotherspoon,[11] Philippe Gaulard,[9,*] and Luc Xerri[12,*]

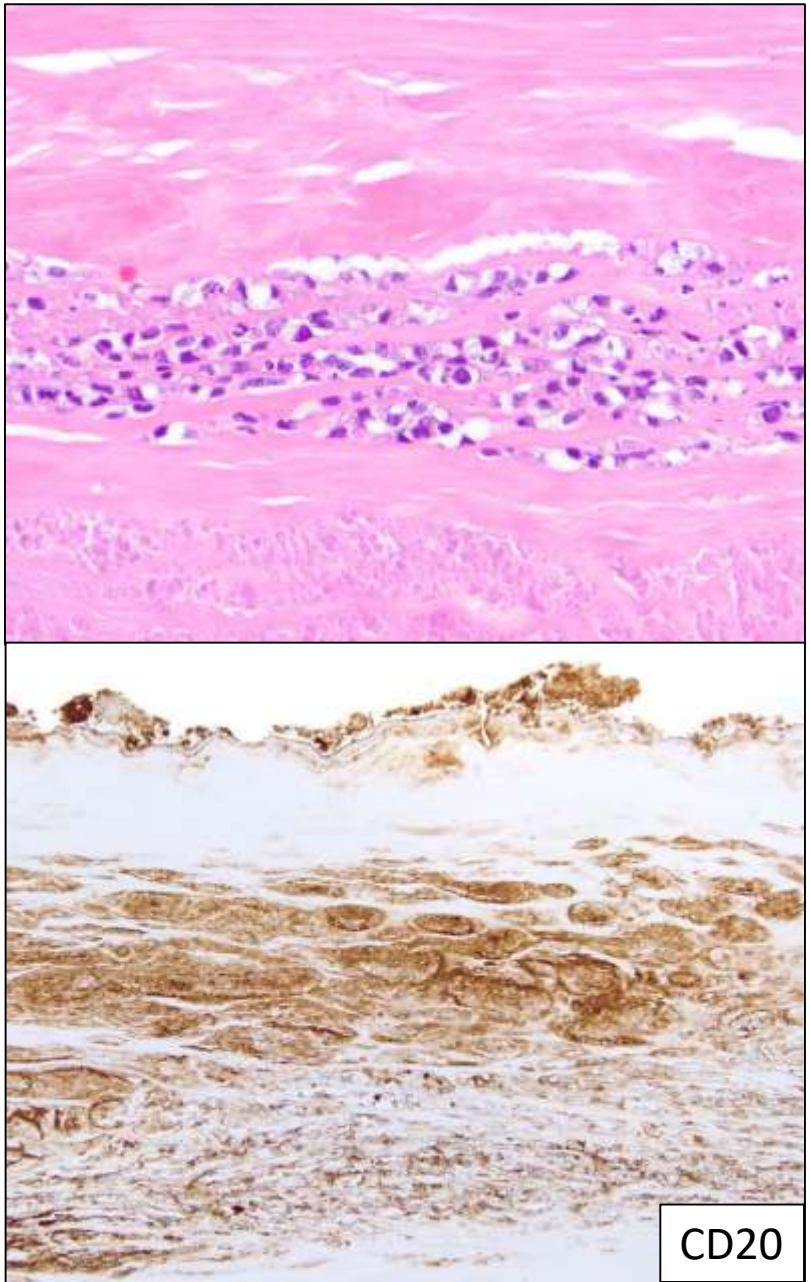
BIA-EBV positive DLBCL

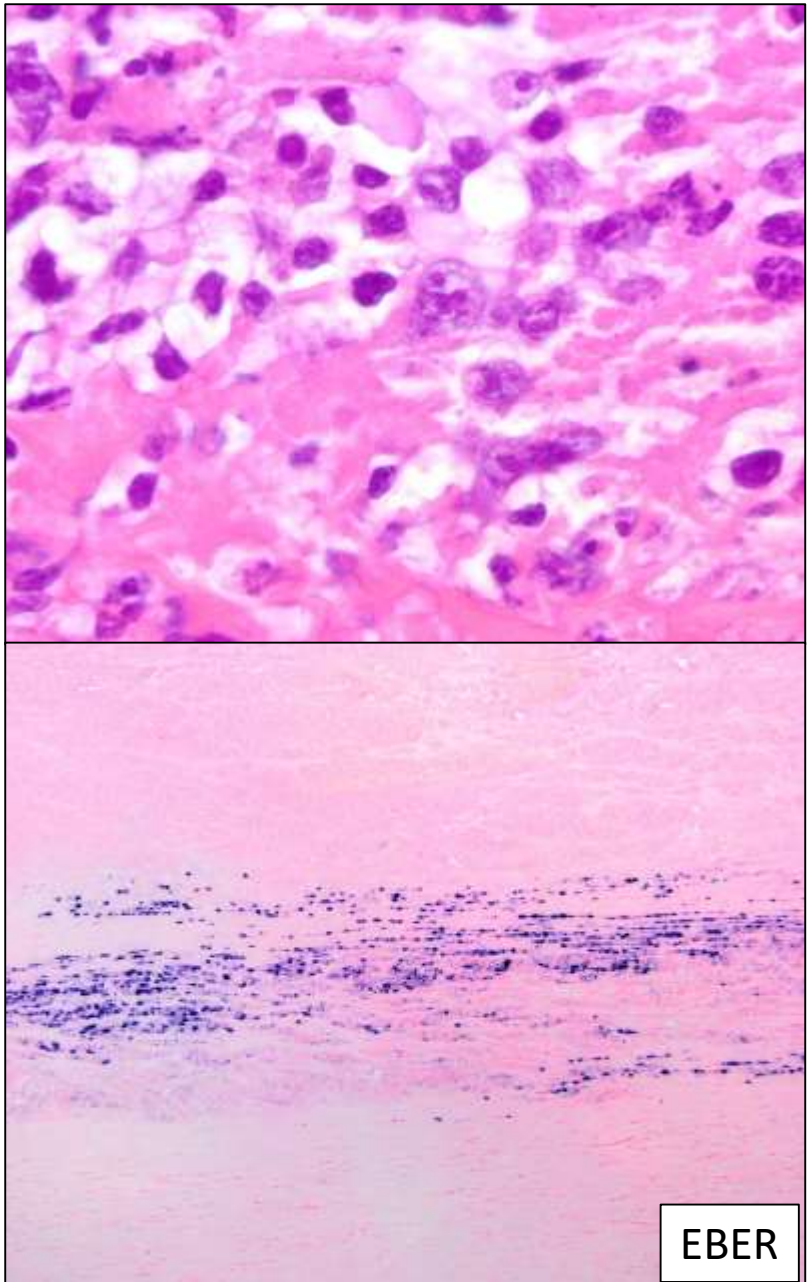
Features	BIA-EBV DLBCL	BIA-ALCL
T cell markers	N	Y
B cell markers	Y	N
EBV	Y	N
CD30	Weak/variable	Strong, uniform
PCR - clonality	B cell	T cell
Thicker capsule	Y	N
Lymphoid aggregates	Y	N
Foamy histiocytes	Y	N

Abstracted from: Medeiros et al. *Mod Path*, 2021.

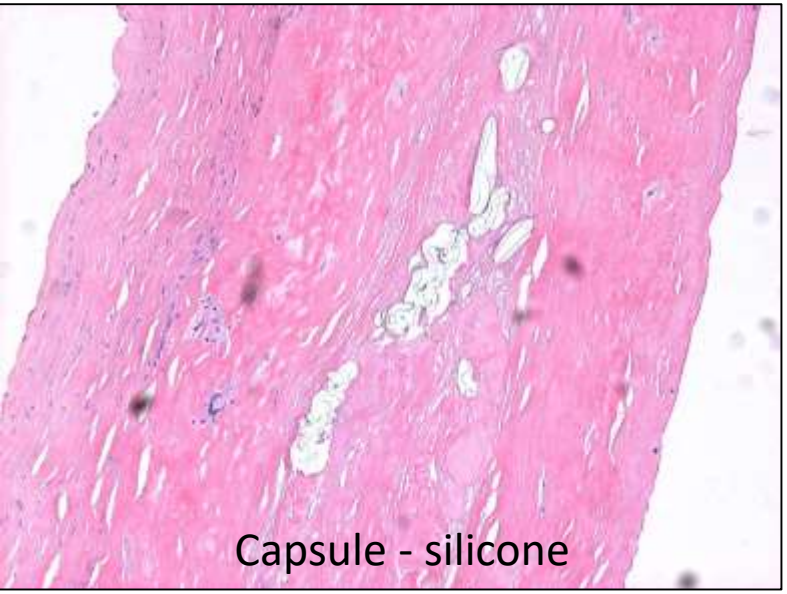
EBV+ BIA-DLBCL

Images courtesy Jeff Medeiros

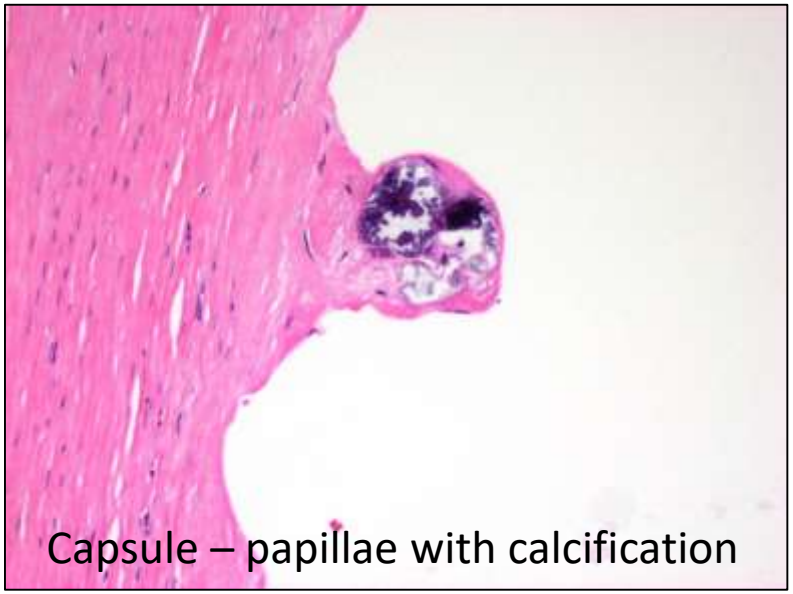




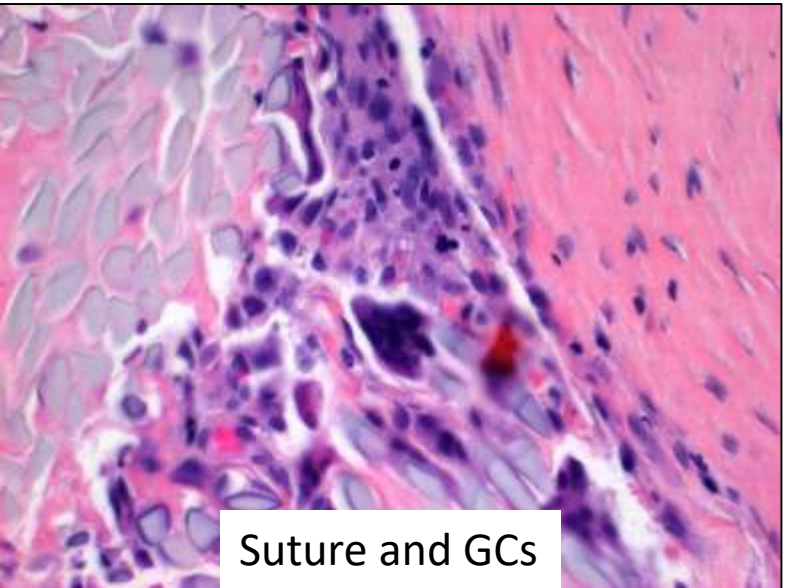
Some other changes seen in breast implant capsules



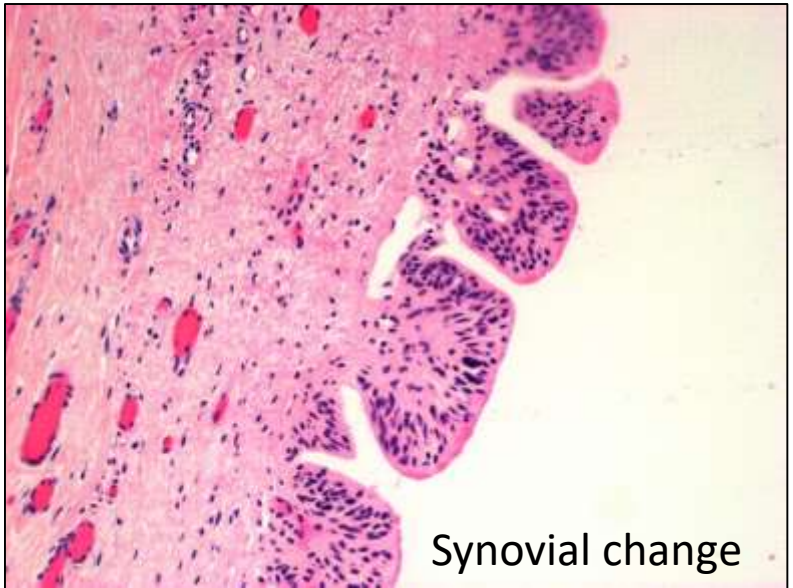
Capsule - silicone



Capsule – papillae with calcification



Suture and GCs



Synovial change

Characteristics and Treatment of Advanced Breast Implant–Associated Anaplastic Large Cell Lymphoma

Meredith S. Collins, MD
Roberto N. Miranda, MD
L. Jeffrey Medeiros, MD
Marcelo Pinheiro Silva de Meneses, MD
Swaminathan P. Iyer, MD
Charles E. Butler, MD, FACS
Jun Liu, PhD
Mark W. Clemens, MD, FACS

Houston, Texas; and Aracaju, Brazil

Background: Breast implant–associated anaplastic large cell lymphoma (BIA-ALCL) most commonly follows an indolent course; however, a subset of patients display more advanced disease marked by recurrent and disseminated growth refractory to treatment. This study evaluated outcomes of advanced disease, specifically bilateral disease, lymph node involvement, organ metastasis, and/or disease-related death.

Methods: Published cases of BIA-ALCL from 1997 to 2018 and unpublished cases at the authors' institution were retrospectively reviewed, and patients with advanced disease were selected. Treatment and outcomes were compared against a control of BIA-ALCL subjects without advanced disease.

Results: Thirty-nine patients with advanced BIA-ALCL were identified who

Table 3. Outcomes for BIA-ALCL With and Without Aggressive Features

Outcome	BIA-ALCL Without Aggressive Features (n = 65)	BIA-ALCL With Aggressive Features: Death of ALCL (n = 6)	BIA-ALCL With Aggressive Features: Bilateral Disease (n = 3)	BIA-ALCL With Aggressive Features: Lymphadenopathy (n = 24)
DOD	0 (0)	6 (100)	5 (20.8)	1 (33.3)
DOUD	0 (0)	0 (0)	2 (8.3)	0 (0)
CR	65 (100)	0 (0)	2 (66.7) ($P = 0.045$)	17 (70.8) ($P < 0.001$)

CR, complete remission; DOD, death of disease; DOUD, dead of unrelated disease.

Take home messages

- Prognosis!
  - ALK+, TP63, DUSP22, triple negative
- Breast implant associated ALCL – careful assessment!
- IHC: frequent loss of many markers
  - Consider CD43, cytotoxic markers, EBER (BIA-EBV+DLBCL)