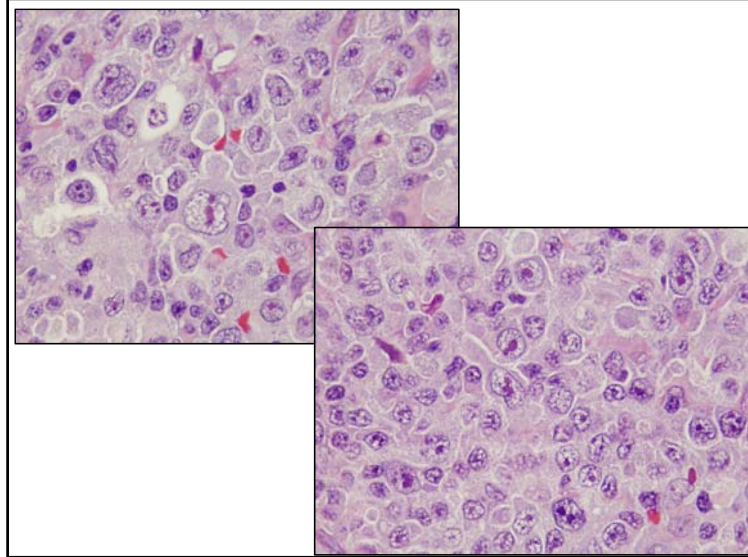
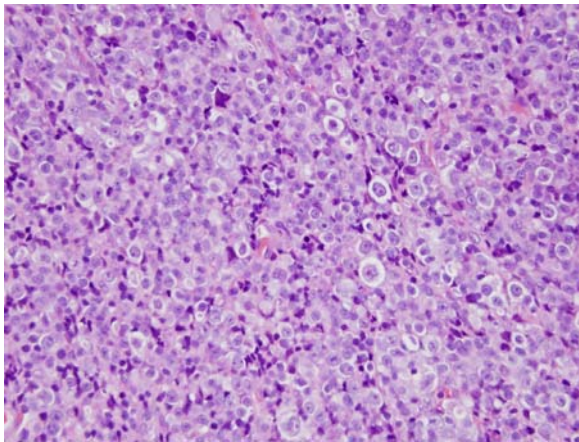
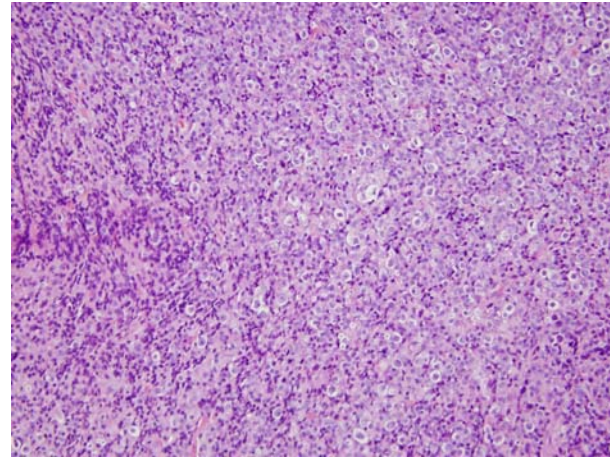


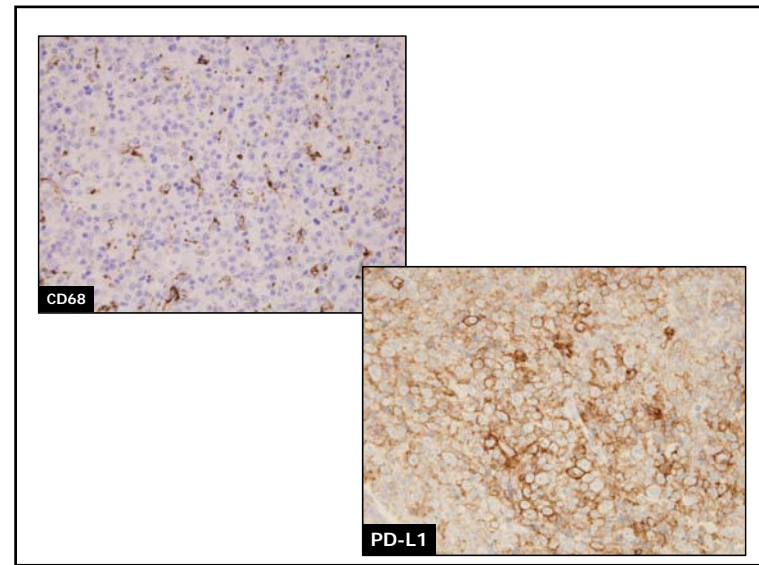
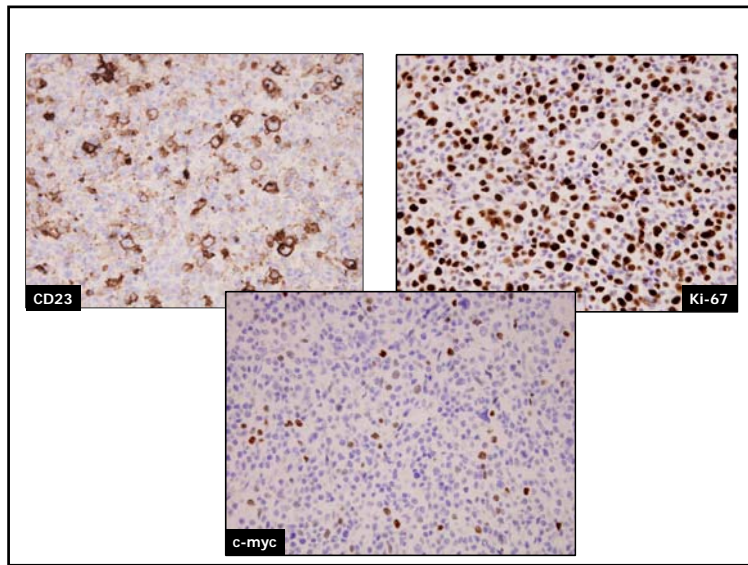
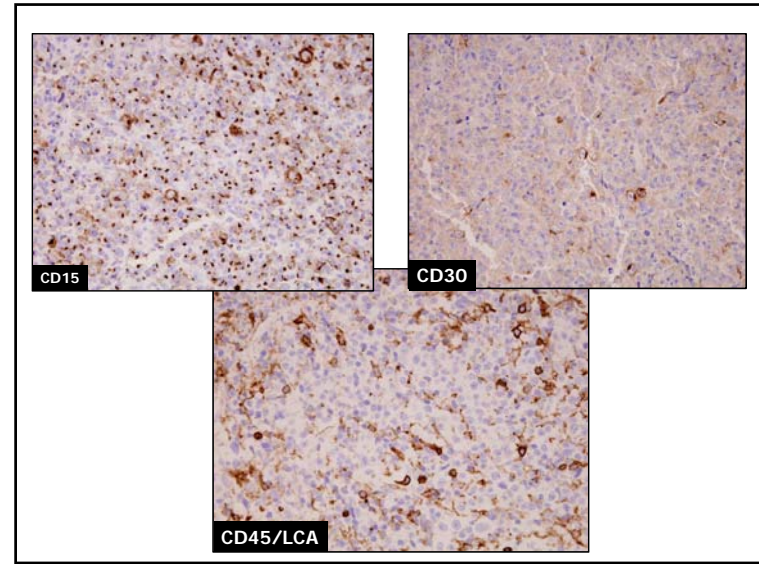
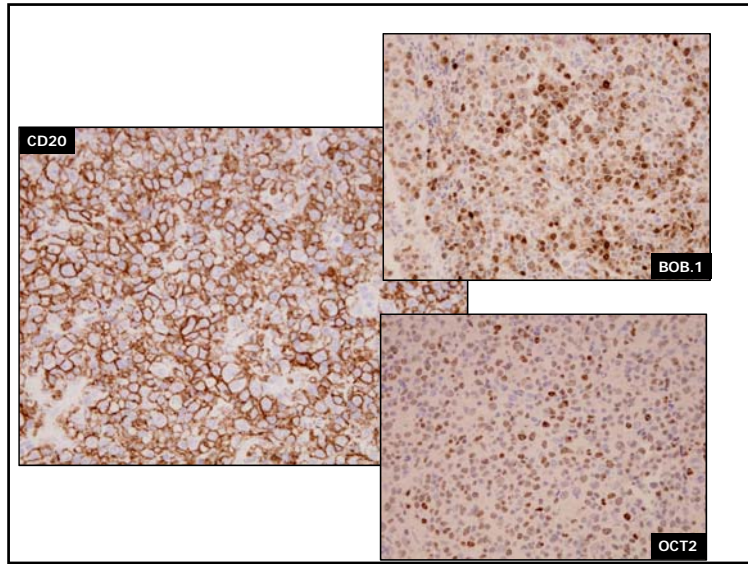
Case History

45-year-old man

He presented with a mediastinal mass, cervical lymphadenopathy, kidney tumors, high serum LDH, and IPI score of 3.

A cervical lymph node was biopsied





Diagnosis

B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classic Hodgkin lymphoma

a.k.a. Mediastinal gray zone lymphoma

**B-cell lymphoma, unclassifiable,
with features intermediate between
diffuse large B-cell lymphoma and
classic Hodgkin lymphoma**

Jaffe E.S.
Stein H.
Swerdlow S.H.
Campo E.
Pileri S.A.
Harris N.L.

“...is a B-cell-lineage lymphoma that demonstrates overlapping clinical, morphologic, and/or immunophenotypic features between CHL and DLBCL, especially primary mediastinal (thymic) large B-cell lymphoma. These lymphomas are most commonly associated with mediastinal disease, but similar cases have been reported in peripheral lymph node groups as the primary site.”

2017 WHO book, p. 342

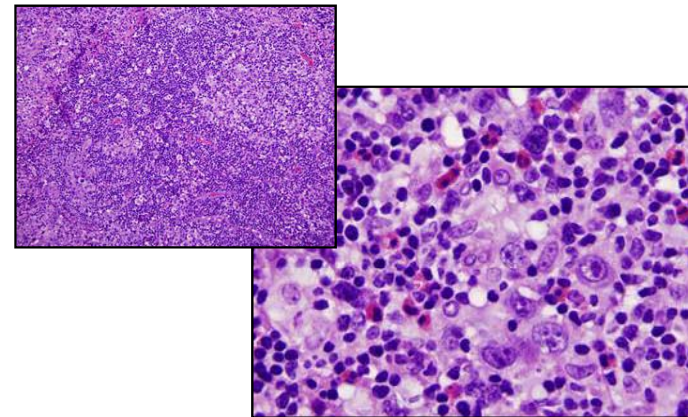
Gray Zone Lymphoma Two Types

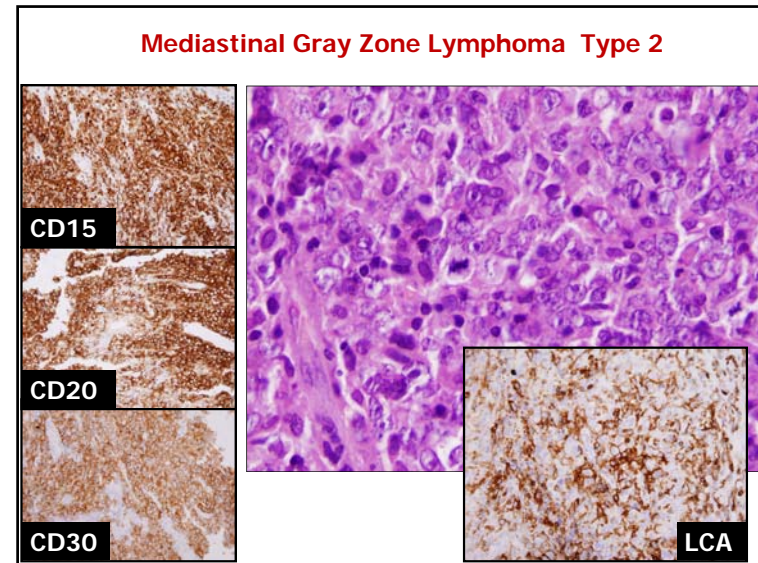
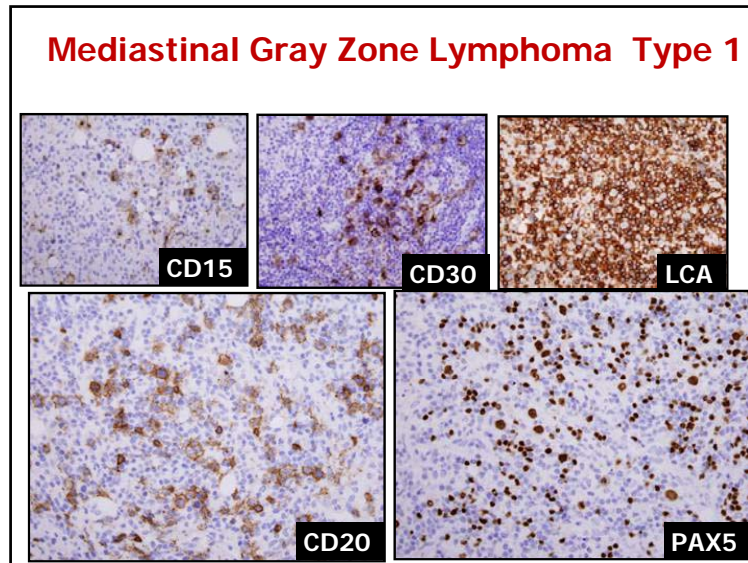
1. “Cases in which the cytological appearance might suggest CHL show preservation of the B-cell program with strong and uniform positivity for CD20 and CD79a. CD30 is usually positive and CD15 may be expressed.”
2. “Cases in which the histological appearance on H&E staining might suggest PMBL show loss of B-cell antigens but positivity for CD30 and CD15.”

“discordance between the cytological appearance and the immunophenotype is common”

2017 WHO book, p. 342

Mediastinal Gray Zone Lymphoma Type 1



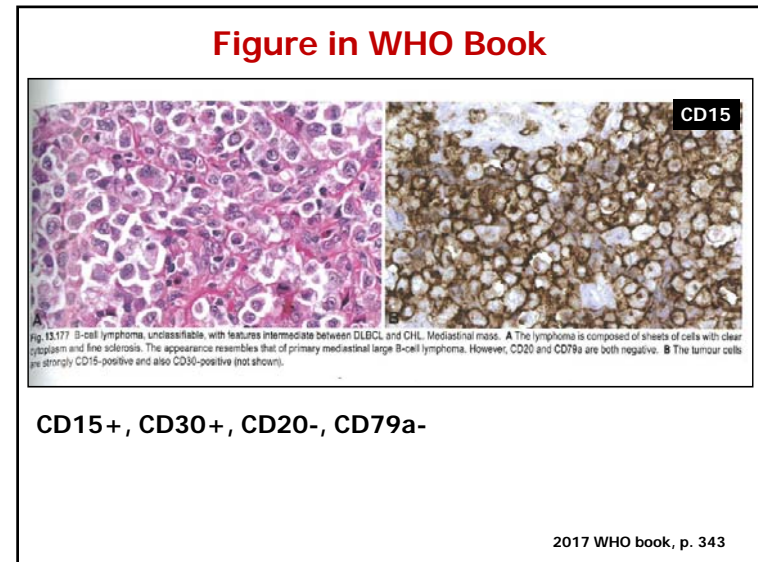


Mediastinal Gray Zone Lymphoma Clinical Features

Men > women
20-40 years

Large mediastinal mass
Supraclavicular lymph nodes +/-
Bulky mass common
SVC syndrome can occur
Direct extension into lung +/-
Can metastasize to liver, spleen, BM

2017 WHO book, p. 342



CHL vs MGZL vs DLBCL What Are Stakes?

Classical HL	ABVD (standard)
DLBCL	R-CHOP + XRT (standard) or DA-EPOCH-R (now popular)
MGZL	DA-EPOCH-R

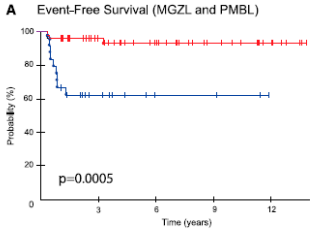
CLINICAL TRIALS AND OBSERVATIONS

A prospective study of mediastinal gray-zone lymphoma

Wyndham H. Wilson,¹ Stefania Pittaluga,² Alina Nicolae,² Kevin Camphausen,³ Margaret Shovlin,¹ Seth M. Steinberg,⁴ Mark Roschewski,¹ Louis M. Staudt,¹ Elaine S. Jaffe,² and Kieron Dunleavy¹

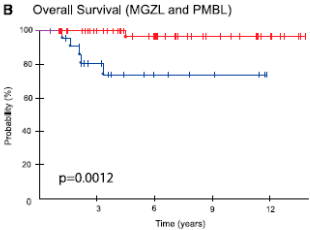
¹Lymphoid Malignancy Branch, ²Laboratory of Pathology, ³Radiation Oncology Branch, and ⁴Center for Cancer Research, National Cancer Institute, Bethesda, MD

A Event-Free Survival (MGZL and PMBL)



p=0.0005

B Overall Survival (MGZL and PMBL)




p=0.0012

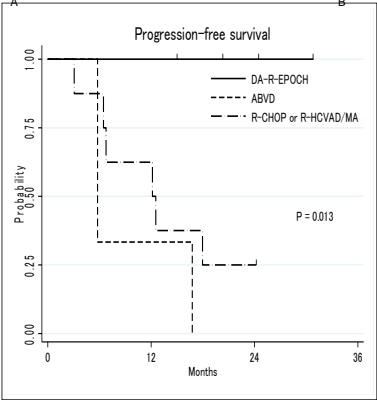
PMBL
MGZL

Blood 124: 1563, 2014

Mediastinal Gray Zone Lymphoma 16 Patients at MDACC



Michelle Fanale, MD




6 R-CHOP
5 DA-EPOCH-R
3 ABVD
2 R-HCVAD-MA

PD-1 Blockade in Mediastinal Gray-Zone Lymphoma

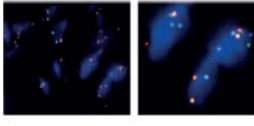
3 pts with GZL treated with pembrolizumab or nivolumab (PD-1 inhibitors)

A FDG-PET Scans of Patient 1



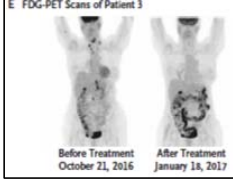
Before Treatment: March 24, 2016
After Treatment: October 20, 2016

B FISH Analysis in Patient 1



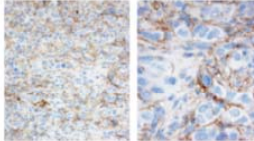
PD-L1 rearrangement

E FDG-PET Scans of Patient 3



Before Treatment: October 21, 2016
After Treatment: January 18, 2017

F Immunohistochemical Analysis in Patient 3



PD-L1 expression

N Engl J Med 377: 89, 2017

Molecular Diagnosis of Primary Mediastinal B Cell Lymphoma Identifies a Clinically Favorable Subgroup of Diffuse Large B Cell Lymphoma Related to Hodgkin Lymphoma

118 / 348 (34%) genes shared between PMBCL and HL

J Exp Med 198: 6, 2003

What is Cell of Origin of Gray Zone Lymphoma?

Two possibilities

1. A cell intermediate in differentiation between classical HL and DLBCL
2. A stem cell that can differentiate into either classical HL or DLBCL

I favor # 2 but both may be true

Gray zone lymphoma with features intermediate between classical Hodgkin lymphoma and diffuse large B-cell lymphoma: Characteristics, outcomes, and prognostication among a large multicenter cohort

Andrew M. Evans,^{1*} Jennifer A. Kanakry,² Laurie H. Sehn,³ Athena Kridharis,⁴ Tatiana Feldman,⁴ Aimee Koel,⁵ Randy D. Gascoyne,⁶ Jeremy S. Abramson,⁷ Adam M. Petrick,⁸ Francisco J. Hernandez-Ilizaliturri,⁹ Zeina Al-Mansour,¹⁰ Camille Adeimy,¹¹ Jessica Hemminger,¹² Nancy L. Bartlett,¹³ Anthony Mato,¹⁴ Paolo F. Caimi,¹⁵ Ranjana H. Advani,¹⁶ Andreas K. Klein,¹⁷ Chadi Nabhan,¹⁸ Sonali M. Smith,¹⁹ Jesus C. Fabregas,²⁰ Isidore S. Lossos,²¹ Oliver W. Press,²² Timothy S. Fenske,²³ Jonathan W. Friedberg,²⁴ Julie M. Vose,²⁵ and Kristie A. Blum²⁶

112 Patients
Median age = 39y
M/F = 1.5
IPI 0-2 66%
48 (43%) mediastinal
64 (57%) non-mediastinal

64 (57%) non-mediastinal patients
Older (50 y)
>1 extranodal site
BM+
Less often bulky

OS and PFS similar for mediastinal and non-mediastinal groups
Rituximab associated with better outcomes

Am J Hematol 90: 778, 2015

Mediastinal Gray Zone Lymphoma
Best Test for Diagnosis

Sensitivity 100%
Specificity 100%

Send it to Dr. Jaffe

Dear Dr. Medeiros,

Email 9-29-17

This is Michael, I am finally feeling almost normal. I ended up doing dose adjusted R-EPOCH and did level 3 on both my 3rd and 4th treatments before my blood levels finally tanked. NIH protocol would have taken me to level 4 but with my young age they were worried about creating leukemia and figured two doses at level 3 was enough.

In retrospect it was adequate as I experienced cyclical neutropenia every month for 6 months after chemo with one emergency room visit and the need for additional nuplasta shots. The cancer is totally gone as far as the petscan last year and my blood levels are back to normal. Even all my enlarged lymph nodes (5 1/2"x6"x1 1/2" tumor between rib cage and heart) shrunk back to normal.

Quite an ordeal I look back on fondly. It is good to have significance brought into focus early in life and see the hand of God orchestrating your life.

Feel free to contact me or share my story or number to any of your patients you think I may be able to encourage.