EUROPEAN HEMATOLOGY ASSOCIATION

EHA-ISHBT Hematology Tutorial

Self-assessment Case – **High Grade Lymphoma - DLBCL - Diagnostics and Treatment**

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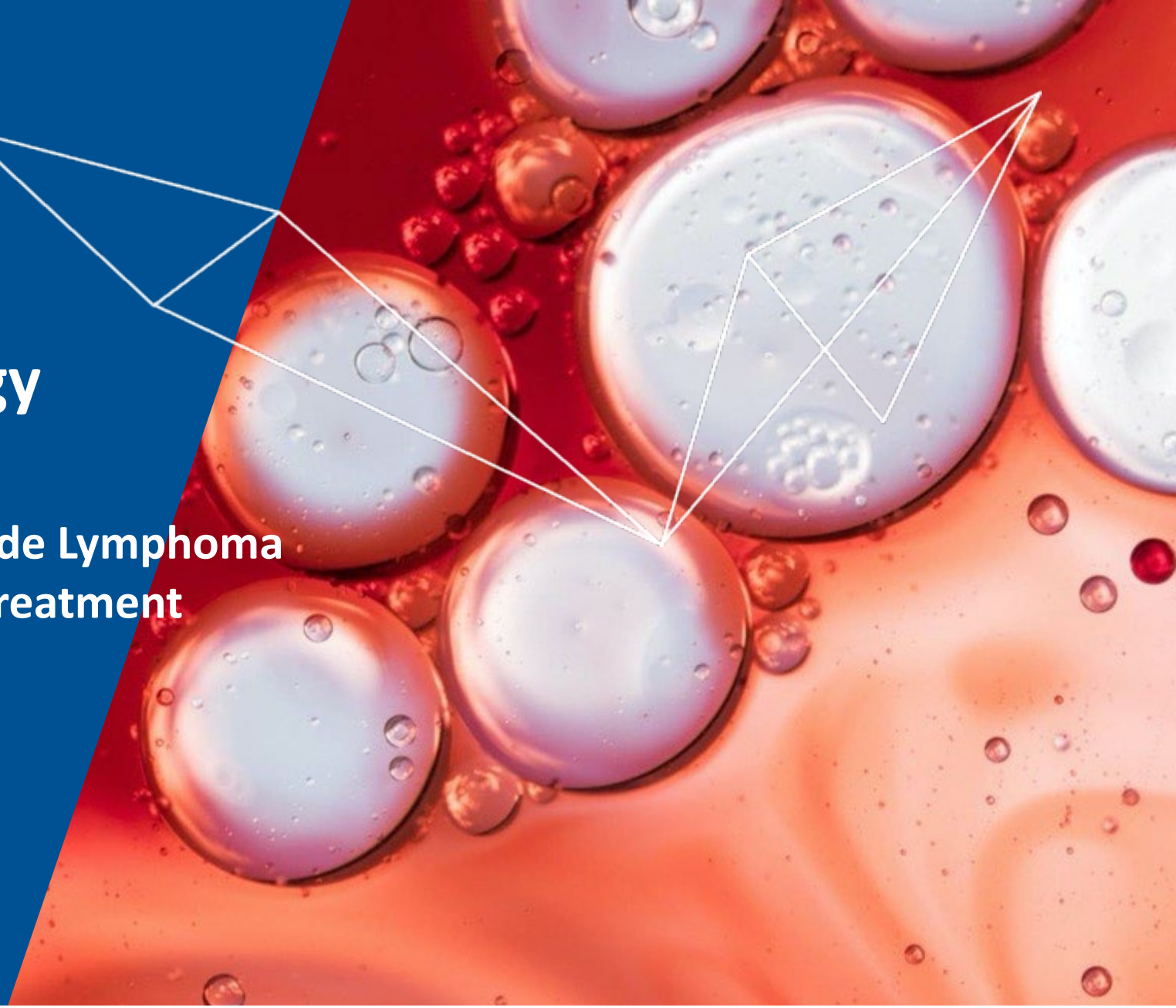
Hyderabad, India
March 1-3, 2024

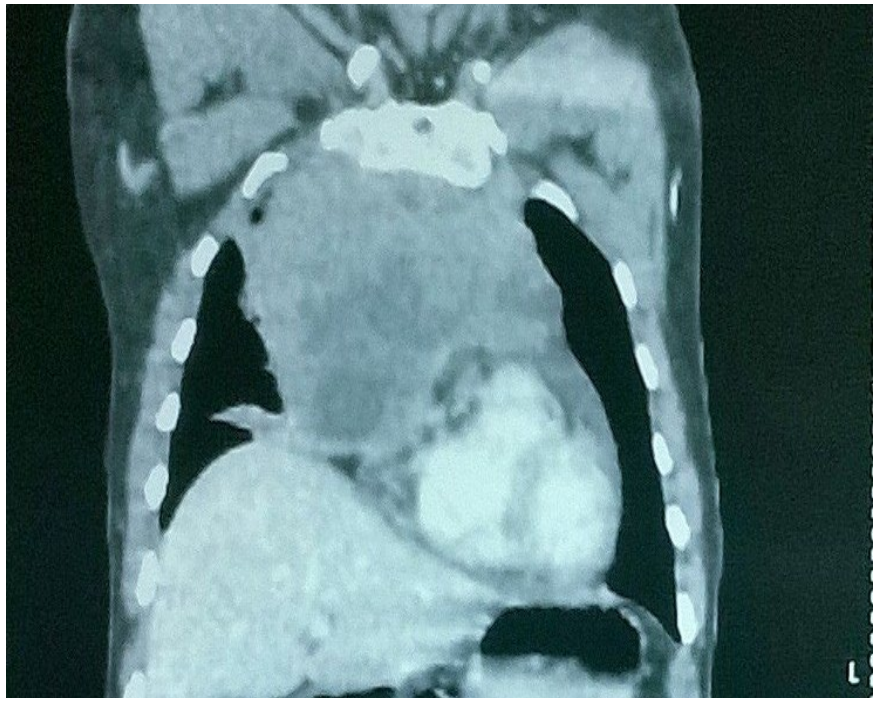


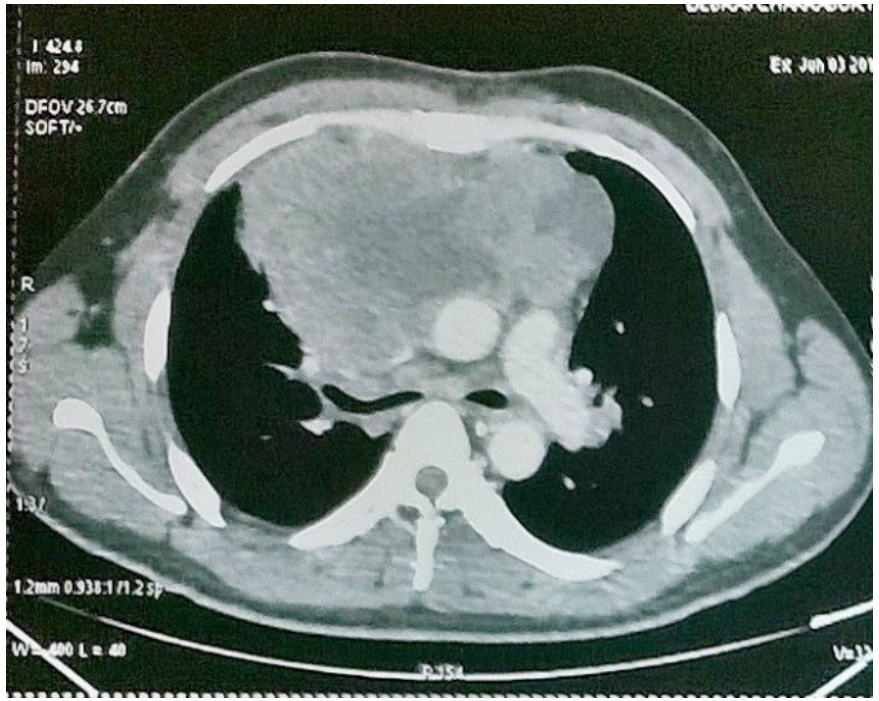
Case 1

- A 21-year-old male presented with a progressive dry cough, heaviness of head, and breathlessness on exertion for one month .
- No history of fever or significant weight loss.
- He was evaluated elsewhere, at that time a chest radiograph had revealed a large mediastinal mass; he was referred to our hospital.

- Physical examination revealed tachypnea, engorged neck veins, dilated veins on the anterior chest wall, facial flushing and swelling, and no palpable peripheral lymphadenopathy or hepatosplenomegaly.
- He was suspected to have superior vena cava obstruction (SVCO) syndrome and was admitted. CT scan of chest was done.
- FBC showed
  - Hb 145 g/l
  - MCV 94 fl
  - WBC 5.7 x 10^9/l; N 69% L 24%, M0 7%
  - Platelet count 251 x 10^9/l
- Liver, Kidney function tests were normal. Serum LDH was 260 (110-220)

CT chest: large mediastinal mass





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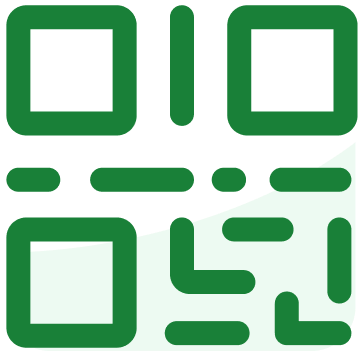

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Q1) Concerning superior vena cava obstruction syndrome which statement is incorrect?

1. An intrathoracic malignancy is responsible for 60 to 85 % of cases of SVC syndrome
2. Non malignant causes of SVCO includes indwelling intravascular devices, post radiation fibrosis, fibrosing mediastinitis
3. Classical clinical features are facial swelling, dyspnea, and cough
4. Endovascular recanalization with or without stenting is a faster way to relieve symptoms compared with Radiation therapy
5. Hodgkin lymphoma is a common cause of SVC syndrome

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7.31 Concerning superior vena cava obstruction syndrome which statement is incorrect?

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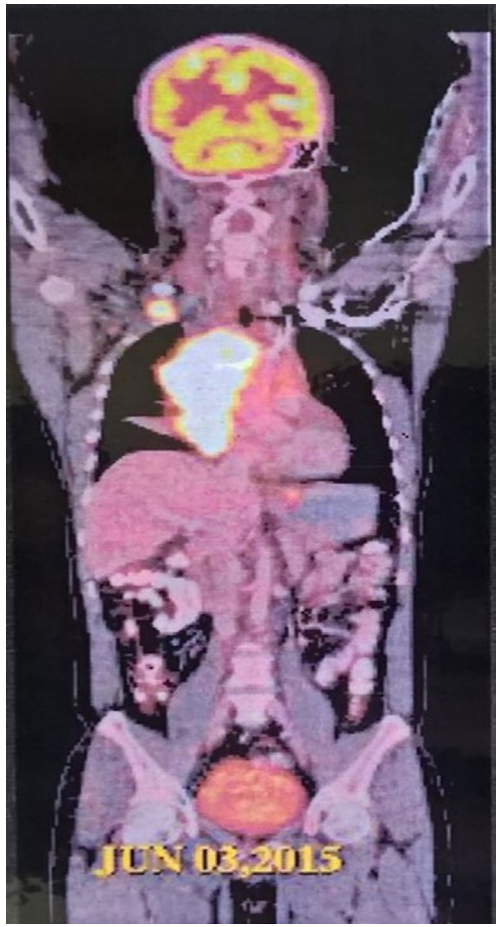
CT guided biopsy from mediastinal mass

- Diffuse lymphoid proliferation of intermediate-size atypical cells positive for **CD20, CD79A, PAX5, CD30 (dim), MUM1, BCL2, and BCL6,** and negative for CD10, BCL1, and EBER.

PET/CT scan showed a bulky anterior mediastinal mass with SUV_{max} of 24.1 and subcarinal and right hilar adenopathy. However, no evidence of disease was observed below the diaphragm



Q2) In primary mediastinal B cell lymphoma which statement is incorrect?

1. PMBCL arises from germinal center or post-germinal center thymic B lymphocytes
2. PMBCL comprises 7% of diffuse large B cell lymphomas (2.4% of all non-Hodgkin lymphomas)
3. There is a female predominance and a median age at diagnosis in the third to fourth decade
4. Present with a locally invasive anterior mediastinal mass originating in the thymus, with superior vena cava (SVC) syndrome
5. Bone marrow involvement is common

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7.32 In primary mediastinal B cell lymphoma which statement is incorrect?

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Discussion

- PMBL is an **aggressive B cell lymphoma** that is thought to arise from thymic (medullary) B cells.
- It has clinicopathologic features that are distinct from systemic diffuse large B cell lymphoma (DLBCL) and shares some clinical and biologic features with nodular sclerosing **classic Hodgkin lymphoma (cHL)**
- Patients with PMBL may have locally extensive disease in the mediastinum, but usually do not have evidence of distant spread at initial presentation.

Q3) Concerning the immunophenotype of PMBL, which statement is incorrect?

1. Positive for CD19, CD20, CD79a and CD45
2. Negative for CD5 and CD10
3. Negative for CD 30
4. Dim positive for CD 30 in 80% of cases
5. Positive for TRAF-1 and nuclear c-REL

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7.33 Concerning the immunophenotype of PMBL, which statement is incorrect?

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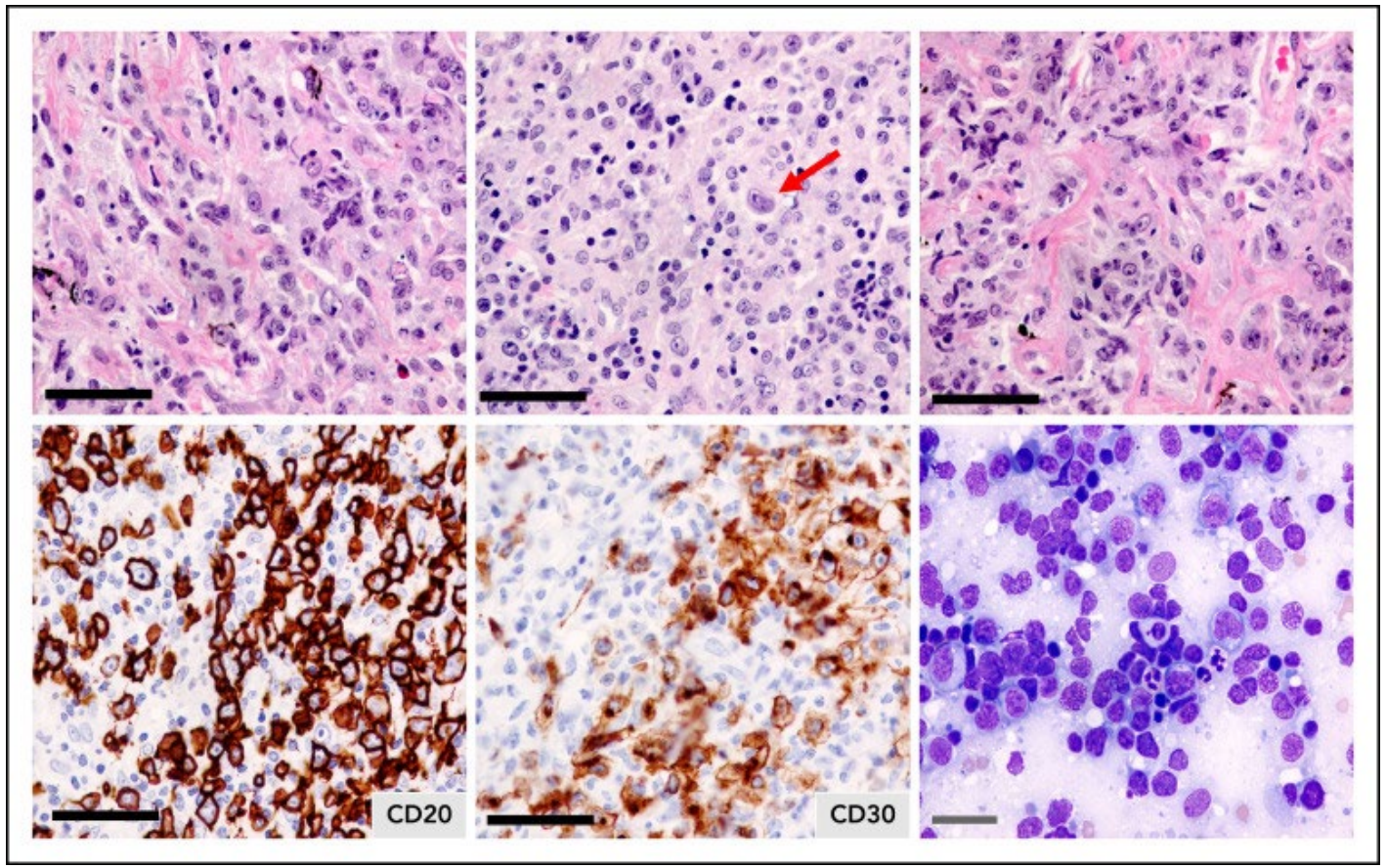
- The diagnosis of PMBL is based on an evaluation of the tumor morphology and immunophenotyping interpreted in the context of the clinical presentation.
- **Staining for pan-B cell markers (CD20, CD79a) is positive**
- Unlike other B-cell lymphomas, PMBCL tumors often lack surface or cytoplasmic immunoglobulin, despite expression of the immunoglobulin co-receptor CD79a.
- **CD10 and CD21 are typically negative**, whereas most cases have a MUM1/IRF4^{+} phenotype with variable BCL6 expression.
- **CD30 is positive in ~80% of cases, but is usually weak** and heterogeneous and CD15 is absent.
- Expression of CD200, CD23, and MAL, a lipid raft component, as well as TRAF1 and nuclear cREL, are characteristic features of PMBCL and distinguish it from DLBCL

PMBL morphology



Savage KJ. Primary mediastinal large B-cell lymphoma. Blood. 2022 Sep 1;140(9):955-970.

Q4) Which pathways are often dysregulated in PMBCL?

1. JAK-STAT and NF-kB pathways
2. Wnt signaling pathway
3. MAPK pathway
4. PI3K-Akt pathway
5. BRCA DNA repair pathway

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7.34 Which pathways are often dysregulated in PMBCL?

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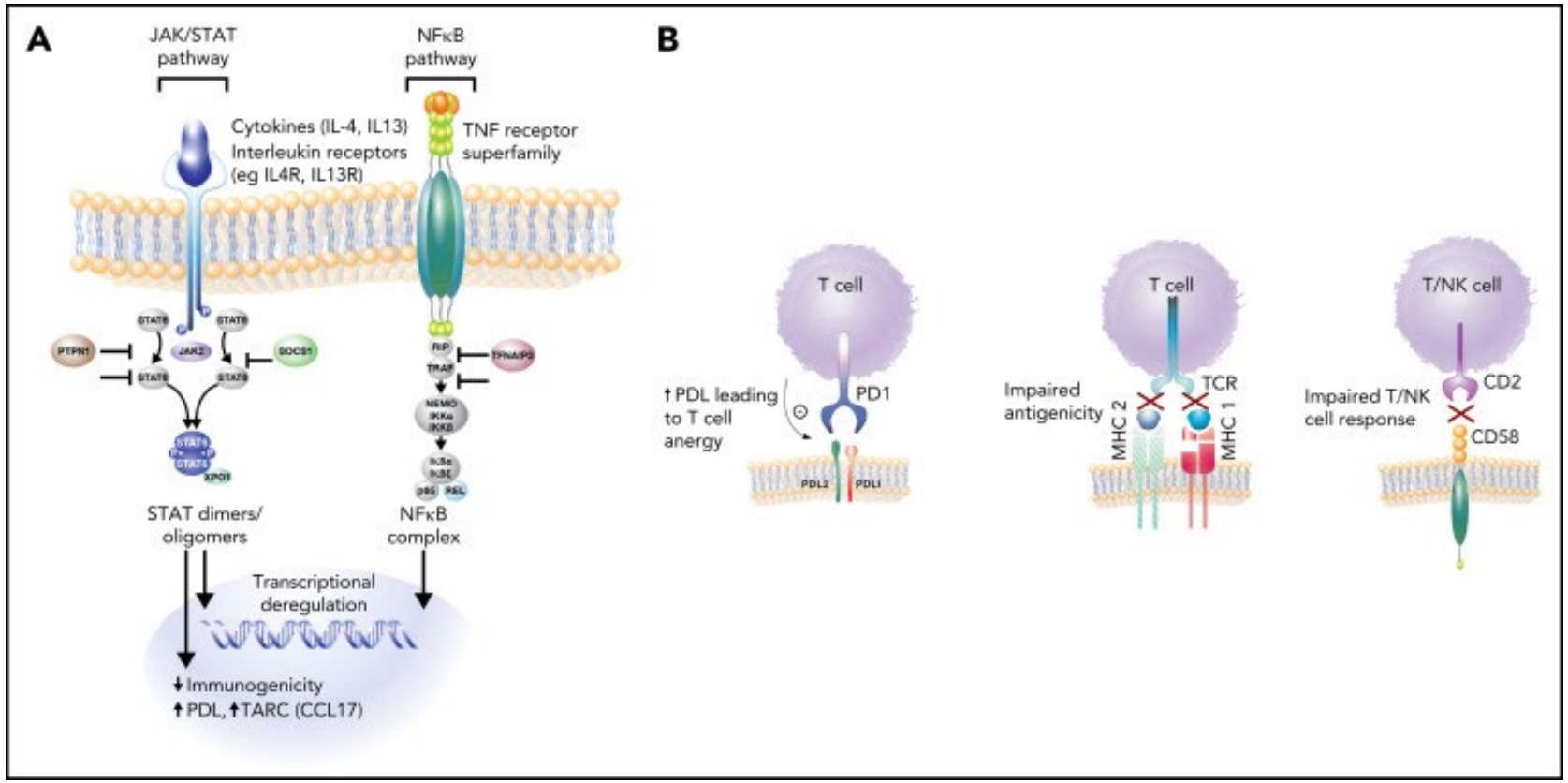
- Molecular hallmarks of PMBCL include constitutive activation of the JAK-STAT and NF-κB pathways and genetic aberrations that lead to a phenotype of immune evasion, all shared features with cHL
- Expression of genes involved in B-cell receptor signaling were decreased

Jak/Stat, NFkB and PDL1 pathways in PMBL



Savage KJ. Primary mediastinal large B-cell lymphoma. Blood. 2022 Sep 1;140(9):955-970.

Q5) Which treatment regimen has shown improved response rates and EFS in PMBCL?

1. CHOP
2. R-CHOP
3. R-da-EPOCH
4. ABVD
5. Bendamustin Rituximab

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7.35 Which treatment regimen has shown improved response rates and EFS in PMBCL?

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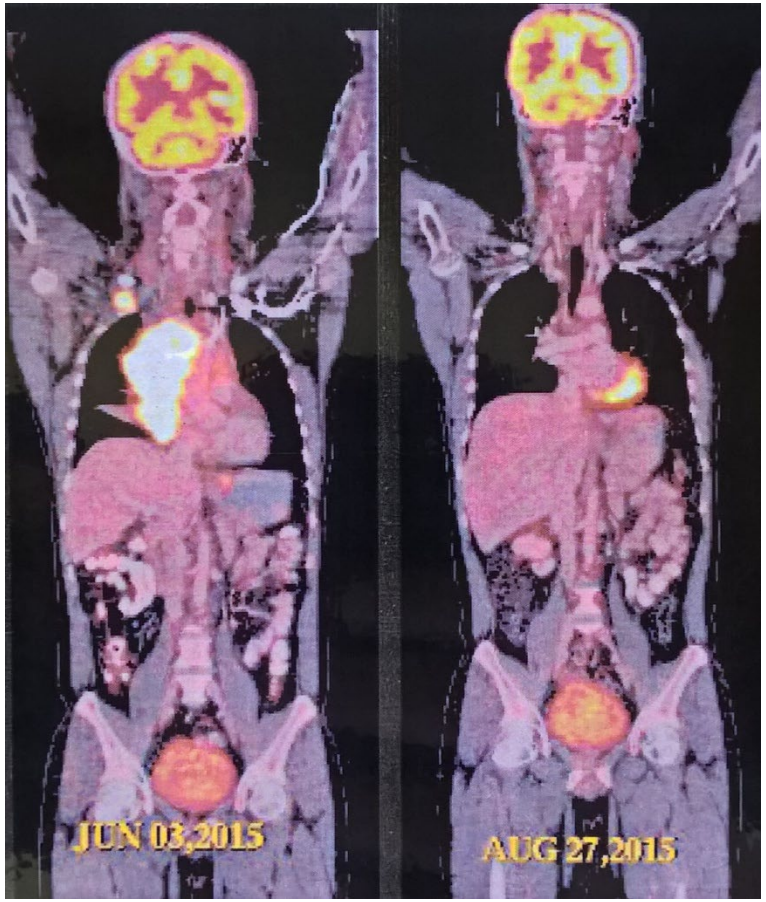
- The optimal treatment of PMBL is unknown and there is variation in clinical practice
  - (DA-EPOCH-R) without radiotherapy
  - R-CHOP with RT
- In a phase 2 National Cancer Institute (NCI) study of DA-EPOCHR in aggressive lymphomas, demonstrated excellent outcomes, with a 5-year event-free survival (EFS) of 93% and OS of 97%, with only 2 patients receiving consolidative RT [2]

- A retrospective multicenter analysis that stratified patients by frontline regimen of either DA-EPOCH-R or R-CHOP showed a higher complete response with DA-EPOCH-R (84% vs 70%; *P*=.046). At 2 years, 89% of patients in the R-CHOP arm and 91% of those in DA-EPOCH-R arm were still alive. [3]
- Da-EPOCH-R would be preferred for patients who wish to avoid RT, such as young (age <30 years) women with disease requiring irradiation of the breast tissue

Case.. RCHOP x 6 f/b RT
A&H after 9 years



Q6) Concerning prognosis of PMBCL in the current era, which statement is incorrect?

1. Da EPOCHR or RCHOP/RT gives a 2 years PFS/OS of around 90%
2. 10-20% patients have relapse refractory disease
3. Relapses are mostly extranodal
4. Most relapses occur late (after 2 years)
5. PDL1 inhibitors have shown efficacy in relapse refractory disease

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7.36 Concerning prognosis of PMBCL in the current era, which statement is incorrect?

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- Relapses tend to be extranodal, including the liver, gastrointestinal tract, kidneys, ovaries, and central nervous system, and almost all occur within two years
- Relapsed disease is treated on the lines of DLBCL; salvage chemo then auto SCT or CAR T cell therapy
- Reports of using PD1 inhibitors as bridge to transplant; pembrolizumab (ORR 45%) or Nivolumab with Brentuximab (ORR 71%)
- The US Food and Drug Administration (FDA) approved pembrolizumab in r/r PMBL for treatment of adult and pediatric patients who have relapsed after ≥2 lines of therapy.

References

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2. Dunleavy K et al. Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. N Engl J Med. 2013 Apr 11;368(15):1408-16.
3. Shah NN et al. R-CHOP versus dose-adjusted R-EPOCH in frontline management of primary mediastinal B-cell lymphoma: a multi-centre analysis. Br J Haematol. 2018 Feb;180(4):534-544.
4. Armand P et al. Pembrolizumab in Relapsed or Refractory Primary Mediastinal Large B-Cell Lymphoma. J Clin Oncol. 2019 Dec 1;37(34):3291-3299
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- Thanks