Breakout #1 – Hematopathology Cases
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Case 1. Primary Mediastinal Large B-Cell Lymphoma (PMBCL)

Definition:
PMBCL is a distinct aggressive B-cell lymphoma arising from thymic B-cells in the anterior mediastinum. It presents with characteristic molecular and clinical features and is often diagnosed in young adults.

Clinical Features:

- **Location**: Anterior mediastinum, with possible invasion of lungs, pleura, or pericardium.
- **Symptoms**: Cough, dyspnea, and superior vena cava syndrome.
- **Prognosis**: Favorable, with 85-90% achieving remission with anthracycline-based chemoimmunotherapy (EPOCH-R).

Histopathology:

- **Architecture**: Diffuse infiltration of large, atypical B cells within a background of fibrotic stroma. The cells are medium to large with clear cytoplasm and vesicular nuclei.
- **Fibrosis**: Often compartmentalizes the tumor cells, creating an alveolar pattern.
- **Necrosis**: Focal necrosis may be present.

Immunophenotype:

- **B-cell markers**: CD20, CD79a, and PAX5 (often weak or absent).
- **Other markers**: CD30 positivity in >80% of cases, with weak and heterogeneous staining.
- **Additional markers**: BCL6 (variable), CD23, CD200, and PD-L1 often positive. CD10 expression is uncommon (<30%).

Key Differential Diagnoses:

Diagnosis	Key Features	Distinguishing Factors
Diffuse Large B-Cell Lymphoma (DLBCL)	Often involves mediastinal lymph nodes and extrathoracic sites.	Lacks thymic involvement and characteristic fibrosis.
Classic Hodgkin Lymphoma (CHL)	CD30 and CD15 positive Reed-Sternberg cells, fibrosis common.	Reed-Sternberg cells and strong CD30 expression in all tumor cells.
Mediastinal Grey Zone Lymphoma	Overlaps between PMBCL and CHL.	Strong and uniform CD30 positivity, loss of B-cell markers.

Case 2. Idiopathic Multicentric Castleman Disease (iMCD)

Definition:
iMCD is a systemic lymphoproliferative disorder characterized by cytokine-driven inflammation and lymph node hyperplasia. The disease manifests in patients without HIV or KSHV/HHV8 infection.

Clinical Features:

- **Locations**: Neck, mediastinum, axilla, and abdomen, often involving multiple lymph nodes.
- **Symptoms**: Fever, anemia, renal dysfunction, and edema.
- **Prognosis**: Treated with anti-IL-6 therapy (siltuximab), but prognosis is worse in iMCD-TAFRO subtype.

Histopathology:

- **Architecture**: Lymph nodes show features like regressed germinal centers, prominent follicular dendritic cells, and increased vascularity.
- **Variants**: Hypervascular, mixed, and plasmacytic types, with plasmacytic infiltration common in iMCD-NOS. iMCD-TAFRO shows more atrophic follicles and high endothelial venules.

Immunophenotype:

- **B-cell markers**: CD20, CD79a positive in the infiltrates.
- **T-cell markers**: CD3 positive, CD8-positive T cells predominate in some cases.
- **Plasma cells**: Polyclonal plasma cells in the interfollicular areas, occasionally with light chain restriction.

Key Differential Diagnoses:

Diagnosis	Key Features	Distinguishing Factors
Polymorphic LPD	Polymorphous infiltrates, systemic involvement.	iMCD presents with cytokine-driven systemic inflammatory features, unlike LPD.
EBV-positive DLBCL	EBV-positive B-cells, systemic involvement.	Lacks the multicentric and systemic inflammatory presentation of iMCD.
POEMS Syndrome	Polyneuropathy, organomegaly, endocrinopathy, M protein.	Unique POEMS features (e.g., polyneuropathy) not seen in iMCD.

Case 3. Lymphomatoid Granulomatosis (LYG)

Definition:
LYG is an EBV-associated, angiocentric, and angiodestructive lymphoproliferative disorder affecting extranodal sites, especially the lungs and CNS.

Clinical Features:

- **Locations**: Lung (most common), CNS, and skin.
- **Symptoms**: Respiratory symptoms like cough, dyspnea, chest pain, and cutaneous or neurological manifestations.
- **Prognosis**: Grade 1-2 often treated with immune modulation; Grade 3 lesions require chemotherapy.

Histopathology:

- **Architecture**: Polymorphous infiltrate with small lymphocytes, plasma cells, histiocytes, and large atypical B cells.
- **Angiocentricity**: Characteristic infiltration and destruction of small to medium-sized vessels.
- **Necrosis**: Often central within nodular lesions, especially in higher-grade lesions.

Immunophenotype:

- **B-cell markers**: EBV-positive large B cells, often CD20 positive.
- **T-cell markers**: CD3-positive T cells form the background infiltrate, with CD4+ cells predominating.
- **EBV positivity**: EBER in situ hybridization detects EBV-positive cells in a spectrum of sizes.

Key Differential Diagnoses:

Diagnosis	Key Features	Distinguishing Factors
EBV-positive DLBCL	Monomorphic EBV-positive B cells.	LYG is characterized by angiocentric infiltrate, whereas DLBCL lacks this feature.
Granulomatosis with Polyangiitis	Necrotizing granulomatous vasculitis, systemic vasculitis.	Granulomas absent in LYG, which shows a polymorphous lymphoid infiltrate.
Extranodal NK/T-cell Lymphoma	NK/T cells, EBV positivity, aggressive systemic behavior.	NK/T-cell phenotype (CD56+, CD3ε+) differentiates it from LYG.

Case 4. EBV-positive Mucocutaneous Ulcer (EBVMCU)

Definition:
EBVMCU is a localized lymphoproliferative disorder of mucosal or cutaneous sites, usually in immunosuppressed patients. It is characterized by the presence of EBV-positive large B cells and/or HRS-like cells.

Clinical Features:

- **Location**: Oral mucosa, gastrointestinal tract, skin.
- **Symptoms**: Well-circumscribed, shallow ulcers, often painful but without systemic symptoms.
- **Prognosis**: Generally regresses with withdrawal of immunosuppression or spontaneous resolution.

Histopathology:

- **Architecture**: Ulcers are well-demarcated, with a polymorphous infiltrate of small lymphocytes, plasma cells, and EBV-positive large B cells.
- **Necrosis**: Often prominent, with angiocentric involvement and occasional thrombosis.
- **HRS-like cells**: EBV-positive, resembling classic Hodgkin cells.

Immunophenotype:

- **B-cell markers**: CD20 and CD30 positive in EBV-positive large B cells, PAX5 positive.
- **T-cell markers**: CD3-positive T cells form a surrounding band at the ulcer base.
- **EBV detection**: EBER-positive large cells in the ulcer base.

Key Differential Diagnoses:

Diagnosis	Key Features	Distinguishing Factors
Polymorphic LPD	Polymorphous infiltrate, systemic involvement.	EBVMCU remains localized and lacks systemic spread.
EBV-positive DLBCL	Monomorphic large B-cells, systemic involvement.	DLBCL shows widespread involvement, unlike EBVMCU.
Extranodal NK/T-cell Lymphoma	Angiocentric infiltrate with EBV-positive NK/T-cells.	NK/T-cell phenotype absent in EBVMCU.

Case 5. Plasmablastic Lymphoma (PBL)

Definition:
PBL is an aggressive B-cell lymphoma with plasmablastic morphology, commonly seen in immunocompromised patients, especially those with HIV.

Clinical Features:

- **Location**: Oral cavity, gastrointestinal tract, soft tissues, and skin.
- **Symptoms**: Rapid growth, necrosis, painful swelling, and frequent ulceration.
- **Prognosis**: Poor prognosis with median survival of 6-32 months; high MYC expression is associated with worse outcomes.

Histopathology:

- **Architecture**: Sheets of large, atypical plasmablastic cells with high mitotic activity and starry-sky pattern due to tingible body macrophages.
- **Plasmablastic morphology**: Cells with abundant cytoplasm, eccentric nuclei, and prominent nucleoli, resembling immunoblasts.

Immunophenotype:

- **B-cell markers**: CD20 negative, PAX5 absent or weakly positive.
- **Plasma cell markers**: CD138, CD38, MUM1 (IRF4) positive.
- **MYC**: Overexpression of MYC protein in most cases, often associated with MYC rearrangements.

Key Differential Diagnoses:

Diagnosis	Key Features	Distinguishing Factors
Diffuse Large B-Cell Lymphoma (DLBCL)	Retains CD20, PAX5 expression, lacks plasmablastic features.	PBL lacks CD20 and expresses plasma cell markers (CD138, MUM1).
Plasmablastic Transformation of PCM	History of plasma cell myeloma, CRAB features.	Prior PCM diagnosis and typical PCM genetic abnormalities differentiate it from PBL.
ALK-positive Large B-Cell Lymphoma	ALK-positive large B-cells, more common in younger patients.	ALK expression present in ALK-positive lymphoma, absent in PBL.

Key Take Home Points

1. **Histopathology is Key**: Each entity has distinct histopathological patterns that are critical for diagnosis—such as the angiocentric infiltrates in LYG or the plasmablastic morphology in PBL.
2. **EBV as a Diagnostic Marker**: EBV positivity is a unifying theme in several of these entities (e.g., PBL, LYG, EBVMCU), underscoring the importance of EBV testing (EBER in situ hybridization) in diagnostic workups.
3. **Immunophenotype Differentiation**: Immunohistochemistry plays a critical role in distinguishing these entities—key markers like CD138 (PBL), CD30 (PMBCL), and PAX5 (PMBCL) are essential for accurate classification.
4. **Prognosis Driven by Pathological Features**: Prognosis in these entities often hinges on histological grade (e.g., LYG) or molecular features (e.g., MYC translocations in PBL), making thorough histopathological examination and ancillary testing crucial for management.
5. **Association with Immune Deficiency**: Entities like PBL, EBVMCU, and iMCD are strongly associated with immunodeficiency states (e.g., HIV, post-transplant), so clinical context is critical in narrowing differential diagnoses.