Differential Diagnosis of Lymphoid Infiltrates of the Lung

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MOVING INFORMATION 106TH ANNUAL MEETING USCAP

Disclosure of Relevant Financial Relationships

Kirtee Raparia, MD has no conflict(s) of interest to disclose.

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Objective

- Common lymphoid infiltrates of the lung: both benign and malignant
- Rare lymphoid infiltrates of the lung

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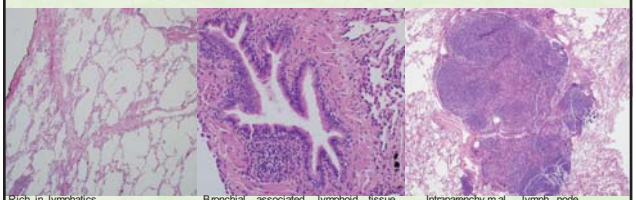
Lung and Lymphatics



Rich in lymphatics | Bronchial associated lymphoid tissue (BALT) | Intraparenchymal lymph node

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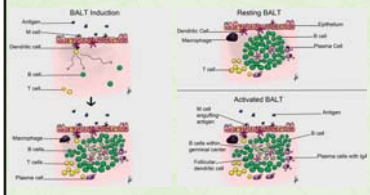
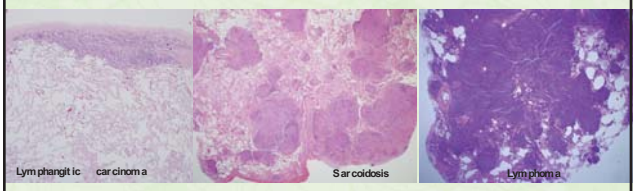
Bronchus-associated Lymphoid Tissue (BALT)

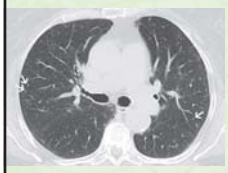


- BALT is a specific type of MALT that is present in the lungs and involved in the immune response to inhaled antigens
- BALT is composed primarily of B cells at the center with peripheral clusters of T cells
- BALT can develop follicles with distinct germinal centers when antigenically stimulated
- BALT is not present at birth, develops in infants and young children.

Lung Disease with lymphatic distribution

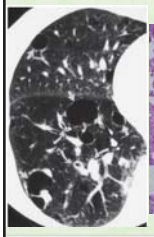


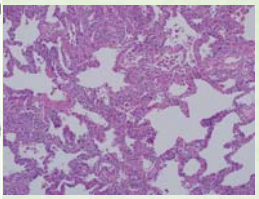
Follicular Bronchiolitis



- Polyclonal hyperplasia and expansion of the BALT from chronic antigen stimulation, resulting in hyperplastic lymphoid follicles primarily composed of polytypic B cells
- More common in males
- Congenital or acquired immunodeficiency, collagen vascular disease

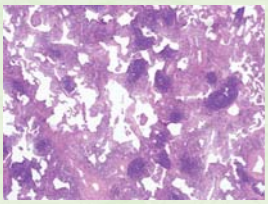
Lymphoid Interstitial Pneumonia





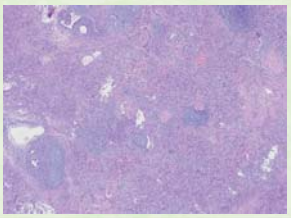
- First described by Leibow and Carrington in 1969 as a diffuse and dense lymphocytic interstitial infiltrate
- Often associated with underlying systemic disease; idiopathic very rare
- Most frequent in females in fifth decade but can present at any age
- Always exclude underlying lymphoproliferative disorder

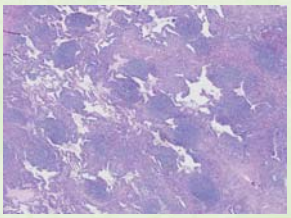
Idiopathic Lymphoid Interstitial Pneumonia



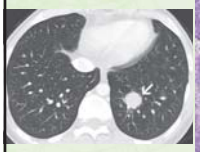
- Clinical course varies from resolution without treatment to progression to end stage disease
- Median survival reported around 11.5 years
- Corticosteroid therapy generally used as first line of therapy
- Progression to lymphoma in limited cases (~5% cases)

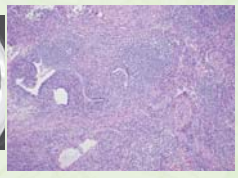
Nodular Lymphoid Infiltrates





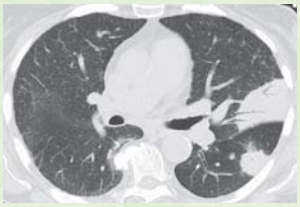
Nodular lymphoid Hyperplasia

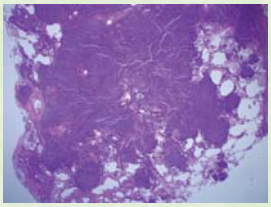


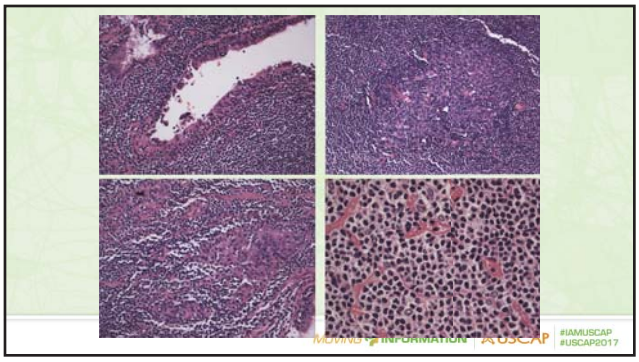


- Adults with altered immune status
- Mixture of B and T cells
- Lymphoepitheli al lesions are common
- Intraepithelial lymphocytes can be B or T cells

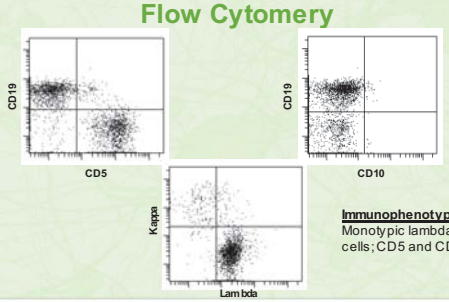
Marginal Zone Lymphoma





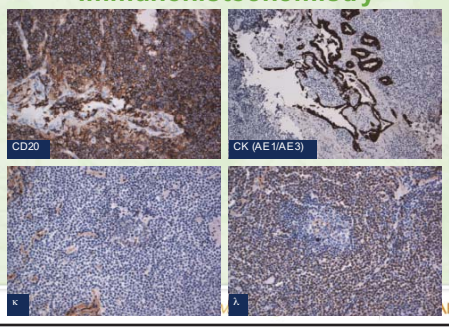


Flow Cytomery



Immunophenotype:
Monotypic lambda positive B cells; CD5 and CD10 negative

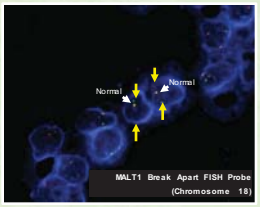
Immunohistochemistry



Molecular / FISH / Cytogenetics

IgH rearranged

Other genetic abnormalities
- t(11;18)
- t(1;14)
- t(14;18)
- t(3;14)
- Trisomy 3, 12, 18
- p53 LOH/mutation



Courtesy: Northwestern Cytogenetics Laboratory

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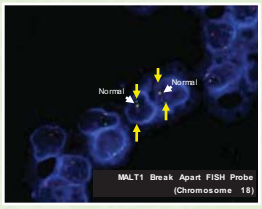


Courtesy: Northwestern Cytogenetics Laboratory

t(11;18) most common in lung and gastric lesions

Importance of Genetic Findings

Gastric MALT lymphoma – correlates with antibiotic response

Antibiotics – Successful in ~75% of cases

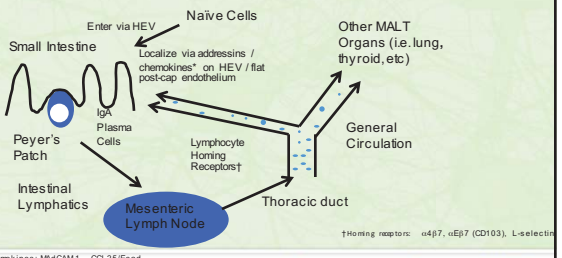
Usually see no response to antibiotic eradication of H. pylori IF
- Stage II_E or greater
- I_{E2} (beyond submucosa) > I_{E1} failure rate
- t(11;18)
- t(1;14)

Pulmonary MALT lymphoma – unknown

Has been rarely treated with antibiotics – clarithromycin
- Regression, but not complete response

Most treated with chemotherapy, immunotherapy and/or radiation

MALT - Imprinting / Circulation Relationship to MALT Lymphoma Sites

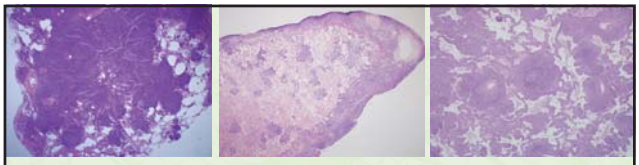


†Homing receptors: α4β7, αEβ7 (CD103), L-selectin

*Addressins/chemokines: MAdCAM-1, CCL25/Ecad, CCL28

Pulmonary Marginal Zone Lymphoma (PMZL)

- Most common primary and secondary lymphoma of the lung (~ 70% of cases)
- First described in 1973
- Median age 50-60 years; M>F
- 80-90% survival at 5 years
- Acquired as secondary response to various antigens
  - Smoking
  - Immunological disease such as Sjogren's syndrome, rheumatoid arthritis, Hashimoto's thyroiditis, systemic lupus erythematosus
  - Infections such as hepatitis C and HIV

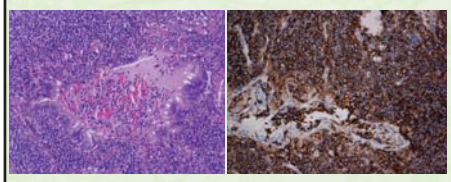


- Solid, dense nodules of lymphoid infiltrate
- Spread at the periphery in an interstitial pattern
- Invasion of bronchi, blood vessels and pleura

Pulmonary Marginal Zone Lymphoma (PMZL)

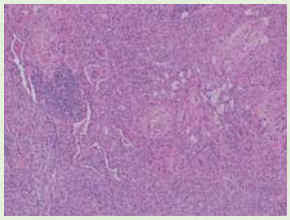
- Pulmonary MZL can be associated with prominent stromal deposition of amyloid in 1% to 6% of cases
- Pulmonary MZL with light chain deposition disease has also been reported, one of them present in an HIV-positive male
- Light chain deposition disease shows deposits similar to amyloid, but these are Congo red negative, whereas amyloid has characteristic Congo red positivity

Lymphoepithelial Lesions



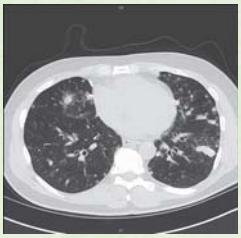
- Bronchial or bronchiolar epithelium
- Significant luminal narrowing
- Both reactive and neoplastic lesions

Inflammatory Myofibroblastic Tumor



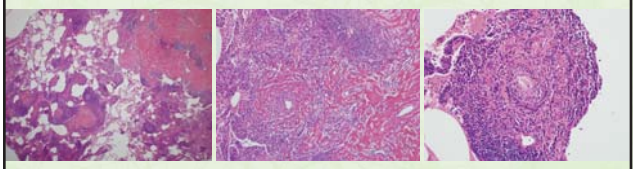
- Lung: most frequent site
- Majority seen in children and young adults with no gender predilection
- Spindle cells admixed with inflammatory elements
- ALK-1 positive in ~ 40% cases

IgG4 related sclerosing disease



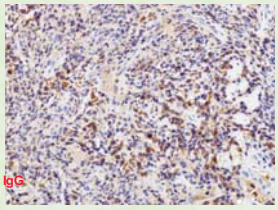
- Multi organ system disease
- Tissue infiltration with lymphocytes, and plasma cells which are IgG4 positive
- Variable amount of fibrosis
- Usually associated with serum IgG4 elevation
- Nearly any organ system can be involved
- Pancreatic/hepatobiliary and salivary/lacrimal gland involvement common
- Lungs involved in < 1/5th of cases overall

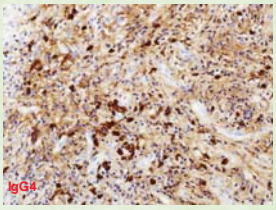
IgG4 related sclerosing disease



Lymphoplasma cytic infiltration
Storiform (whorled) fibrosis
Phlebitis/Vasculitis

IgG4 related sclerosing disease





Proposed Diagnostic Criteria for IgG4RD

1. Clinical or radiologic exam showing characteristic diffuse/localized swelling or masses in single or multiple organs
2. Hematological exam shows elevated igG4 levels (>135mg/dl)
3. Histopathologic exam shows findings consistent with IgG4 related disease (>40% IgG4/IgG cells and > 50/HPF IgG4 cells on SLB, or >20 IgG4 cells on TBBx)
4. Absence of clinical, laboratory or histopathologic features to suggest an alternate diagnosis such as malignancy, granulomatosis with polyangiitis etc.

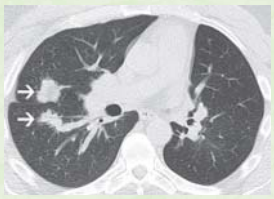
Definite IgG4 related disease: 1+2+3+4

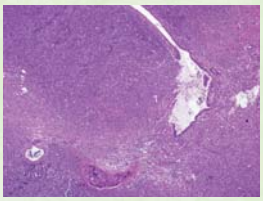
Probable IgG4 related disease: 1+3+4

Possible IgG4 related disease: 1+2+4

Uhmera et al. (2012) 2221-30
Desnpande etal.(2012) 25 1181-1192
Raj et al. CPM 2014: 21(5), 230-238
Culver et al. 201265963-9B.

Diffuse Large B Cell Lymphoma





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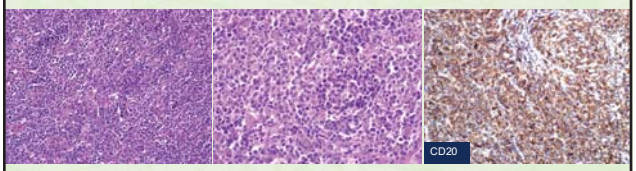
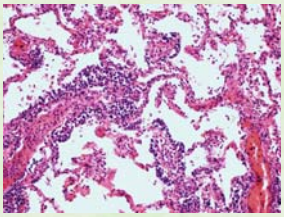
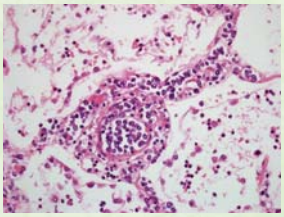


Diffuse Large B Cell Lymphoma

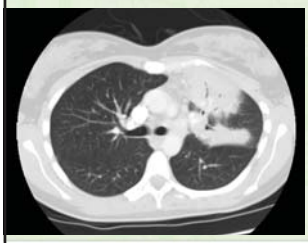
- Primary pulmonary diffuse large B-cell lymphoma is the second most common type of primary pulmonary lymphoma, accounting for approximately 12% to 20% of cases
- It commonly affects adults in the sixth and seventh decades of life, seen in both immunocompromised and immunocompetent patients
- Subset of these lymphomas arise by transformation of preexisting or concurrent MZL, small lymphocytic lymphoma, and follicular lymphoma.
- The immunophenotype of the neoplastic cells is positive for CD19, CD20, and CD79a, and those of germinal center origin also express CD10 and bcl-6

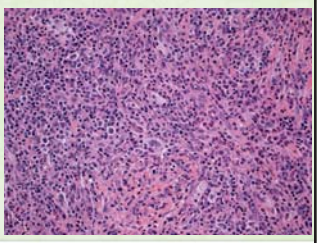
Intravascular Large B Cell Lymphoma (IVLBCL)

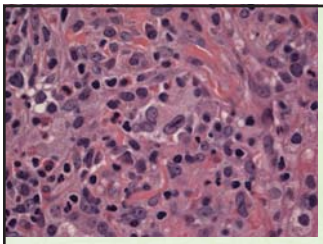


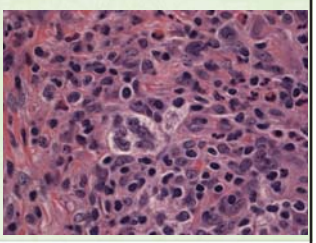


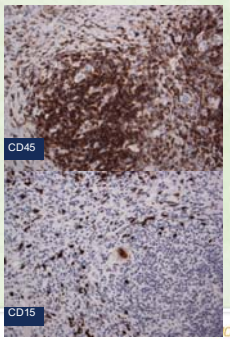
Another Example: Lung Nodule with Lymphoid Cells

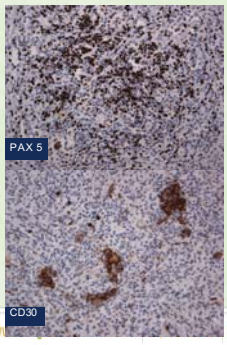








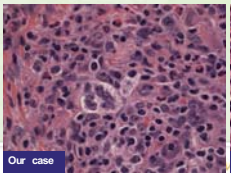


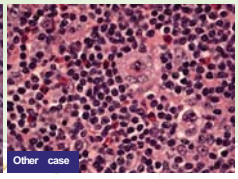


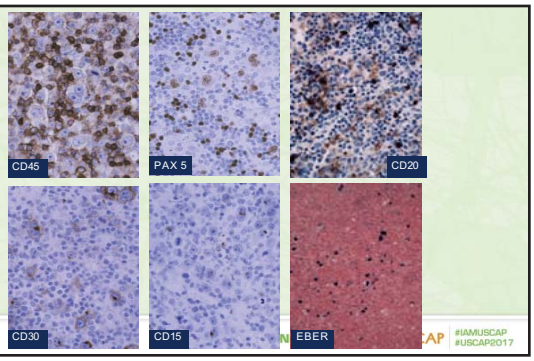
Diagnostic Tools

Flow cytometry, molecular studies not very helpful

Morphology: Reed Sternberg cells and variants
Mixed inflammatory cell population







Primary Pulmonary Hodgkin Lymphoma

- Primary Pulmonary Hodgkin lymphoma: rare entity
- Affects young adults: mean age of 42 years and slight female predisposition
  - Single or multiple parenchymal masses
  - Endobronchial lesions
  - Pneumonia-like consolidation
- No mediastinal lymph node involvement or disease elsewhere

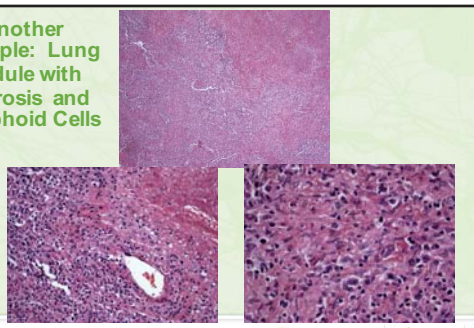
Secondary Involvement of the lung by Hodgkin Lymphoma

- Pulmonary involvement in Hodgkin's disease can occur in 15% to 40% of cases.
- Most patients present with concomitant cervical, mediastinal, or supraclavicular lymph nodes
- Granulomatous response
- Prognosis is favorable (slightly less than nodal)

Factors associated with a poor prognosis

- Age greater than 60 years
- B symptoms
- Multiplicity and bilaterality of lung lesions
- Pleural effusion
- Cavitation

Another Example: Lung Nodule with Necrosis and Lymphoid Cells



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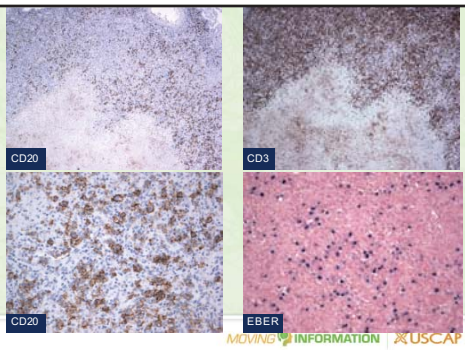

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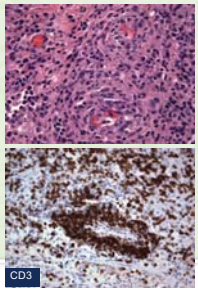
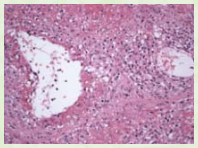
Lymphomatoid Granulomatosis, Grade 2

Morphology





Angiocentric, angiodestructive

Direct invasion of blood vessels by T cells

Chemokines and cytokines from the EBV positive cells

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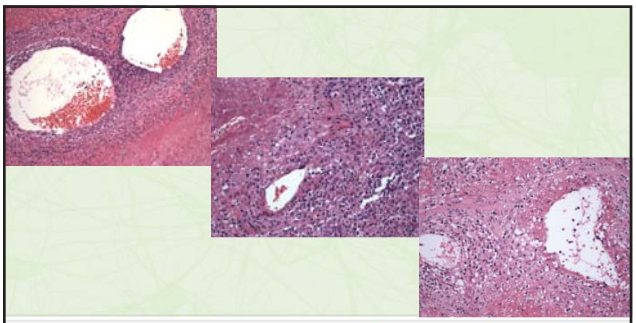

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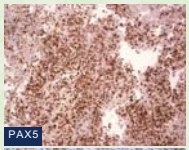
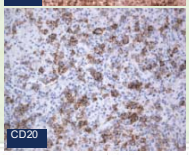
Immunophenotype

EBV positive B cells:
- CD20, PAX5, CD79a positive
- Variably CD30 positive
- CD15 negative

Background of CD3 positive T cells
- Mixture of CD4 and CD8
- CD8 cells are often granzyme B positive





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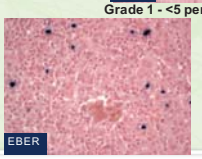
Grading based on the Number of EBV Positive Cells

Grade 1 - <5 per high power field

Grade 2
5 - 20 per high power field



Grade 3
>20 per high power field

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Clinical
Lymphomatoid Granulomatosis

Risk: Underlying immune defect

Sites of involvement:
- Lung - 90%
- Brain - 25%
- Other: Liver, kidney, skin
- Lymph nodes and spleen are rare

Aggressive disease – median survival <2 years

Inflammatory bowel disease: RARE
- Risk for LPDs due to disease probably not increased
- Specific types of drugs increase risk: Thiopurines 3-5x risk

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Other EBV Positive LPDs in the Lung

Immunodeficiency LPDs:
- PID, PTLD, HIV, iatrogenic

EBV positive age related LPDs

EBV positive classical Hodgkin lymphoma (some)

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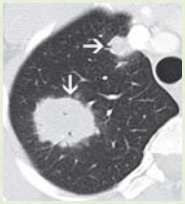
NK/T Cell Lymphoma

- Also an angiocentric, angiodestructive lesion
- Is EBV positive
- Rarely involves the lung (<10%)
- Classic phenotype of neoplastic cells: CD2, cytoplasmic CD3, CD56, EBER

Post transplant Lymphoproliferative Disorder



PTLD of the lung as a complication of liver transplant for autoimmune hepatitis in a 35-year-old woman

Post transplant Lymphoproliferative Disorder

- Encompasses a group of lymphoproliferative disorders occurring in the post stem cell and organ transplant setting that range from benign polyclonal proliferation to malignant monoclonal disease
- Greater than 80% of PTLD cases consist of EBV-infected B-cell proliferations occurring within the first 2 years after transplant
- Histologically, PTLD is a spectrum of lymphoid proliferation.
- The majority of PTLD cases are composed of proliferation of EBV-infected B cells that range from benign polyclonal proliferation to malignant monoclonal proliferation

Conclusion

- Pulmonary lymphoid lesions are diagnostically difficult
- Broad differential exists
- Integrated approach
  - Pathology and radiology
  - Pulmonary pathologist and hematopathologist
  - Routine sections and ancillary studies
    - Immunophenotyping
    - Molecular genetic analysis
    - Cytogenetics
- Correct diagnosis and treatment even in difficult cases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