# Lymphomatoid Granulomatosis

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- Synonym: angiocentric immunoproliferative lesion

# Definition

- Lymphoproliferative disease
- Angiocentric and angiodestructive
- Extranodal sites
- EBV-positive B-cells
- Reactive T-cells (predominant cells)
- Lymph nodes usually spared

# Definition

- Spectrum of histological grade
- Spectrum of clinical aggressiveness (related to the proportion of large B-cells)
- May progress to an EBV-positive DLBCL
- Must be distinguished from NK/T-cell lymphoma, nasal-type

# Epidemiology

- Rare
- Adults, usually
- Children with immunodeficiency disorders
- M:F > 2:1

# Sites of Involvement

- Lung most common site (most patients have pulmonary involvement)
- Skin (25-50%) second most common site
- Kidney (32%)
- Liver (29%)
- Brain (26%)
- Upper respiratory tract
- GI tract
- LN and spleen rarely involved

# Clinical Features

- Patients frequently present with respiratory tract signs and symptoms
  - Cough (58%)
  - Dyspnea (29%)
  - Chest pain (13%)

# Clinical Features

- Common constitutional symptoms
  - Fever
  - Malaise
  - Weight loss
  - Neurologic symptoms
  - Arthralgias
  - Myalgias
  - GI symptoms

# Clinical Features

- Very few patients (<5%) are asymptomatic
- Patients presenting without apparent immunodeficiency symptoms usually are found to have reduced immune function after careful clinical and laboratory analysis

# Etiology

- EBV-driven disease
- Underlying immunodeficiency increases risk
- Predisposing conditions
  - Allogenic organ transplantation
  - Wiskott-Aldrich syndrome (X-linked)
  - HIV
  - X-linked lymphoproliferative syndrome

# Macroscopic

- Lung nodules
  - Variable in size
  - Bilateral
  - Involve mid and lower lung fields
  - Larger nodules
    - Exhibit central necrosis
    - Cavitation often present

Lung

# Macroscopic

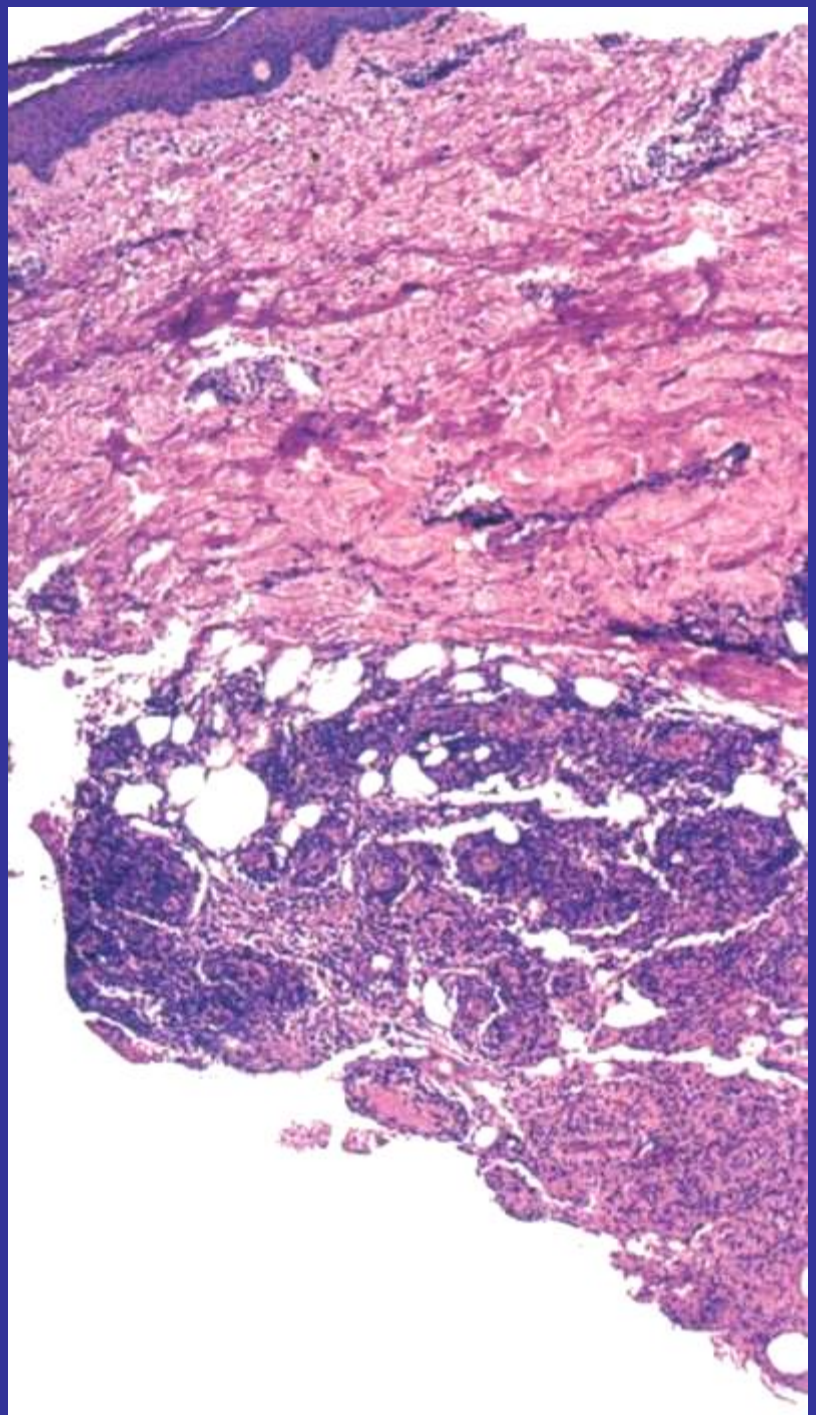
- Kidney and brain
  - Nodular lesions
  - Also central necrosis

Kidney

# Macroscopy

- Skin lesions

- Nodules and papules in dermis and subcutaneous tissue (~85%) sometimes with necrosis and ulceration
- Cutaneous plaques or maculopapular rash (~15%)
- EBV positivity less often seen (especially in plaque lesions)



Skin lesion

# Microscopy

- Angiocentric and angiodestructive polymorphous lymphoid infiltrate
  - EBV-positive B-cells
    - Small numbers
    - Some atypia
    - May resemble immunoblasts
    - May resemble Hodgkin cells
    - May be multinucleated

# Microscopy

- Polymorphous lymphoid infiltrate
- B-cells may have some atypia
- Predominance of reactive T-cells
- Plasma cells
- Immunoblasts
- Histiocytes

# Microscopy

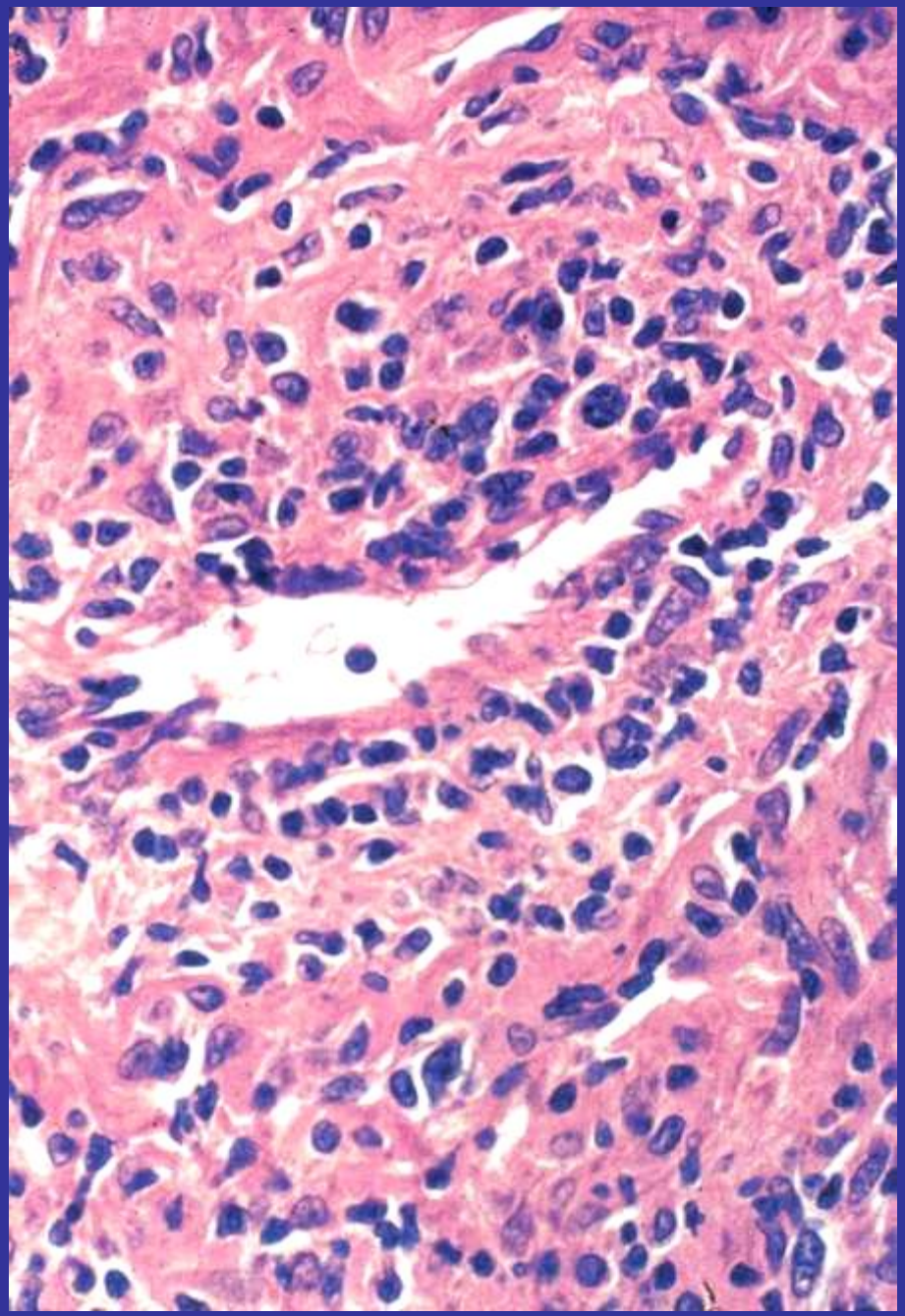
- Prominent vascular changes
  - Lymphocytic vasculitis
    - May compromise vascular integrity, leading to infarction
  - Fibrinoid necrosis
    - Common
    - Mediated by EBV-induced chemokines

# Grading

- Lipford grading scheme
  - Three histologic grades
  - Based on proportion of EBV-positive B-cells relative to reactive lymphocytic background
  - Larger numbers of atypical lymphoid cells associated with worse prognosis

# Grading

- Grade 1
  - Polymorphous lymphoid infiltrate
  - Absent or rare large transformed cells
  - Fewer than 5 EBV-positive cells per HPF by *in situ* hybridization)
  - Necrosis not prominent



Grade 1

# Grading

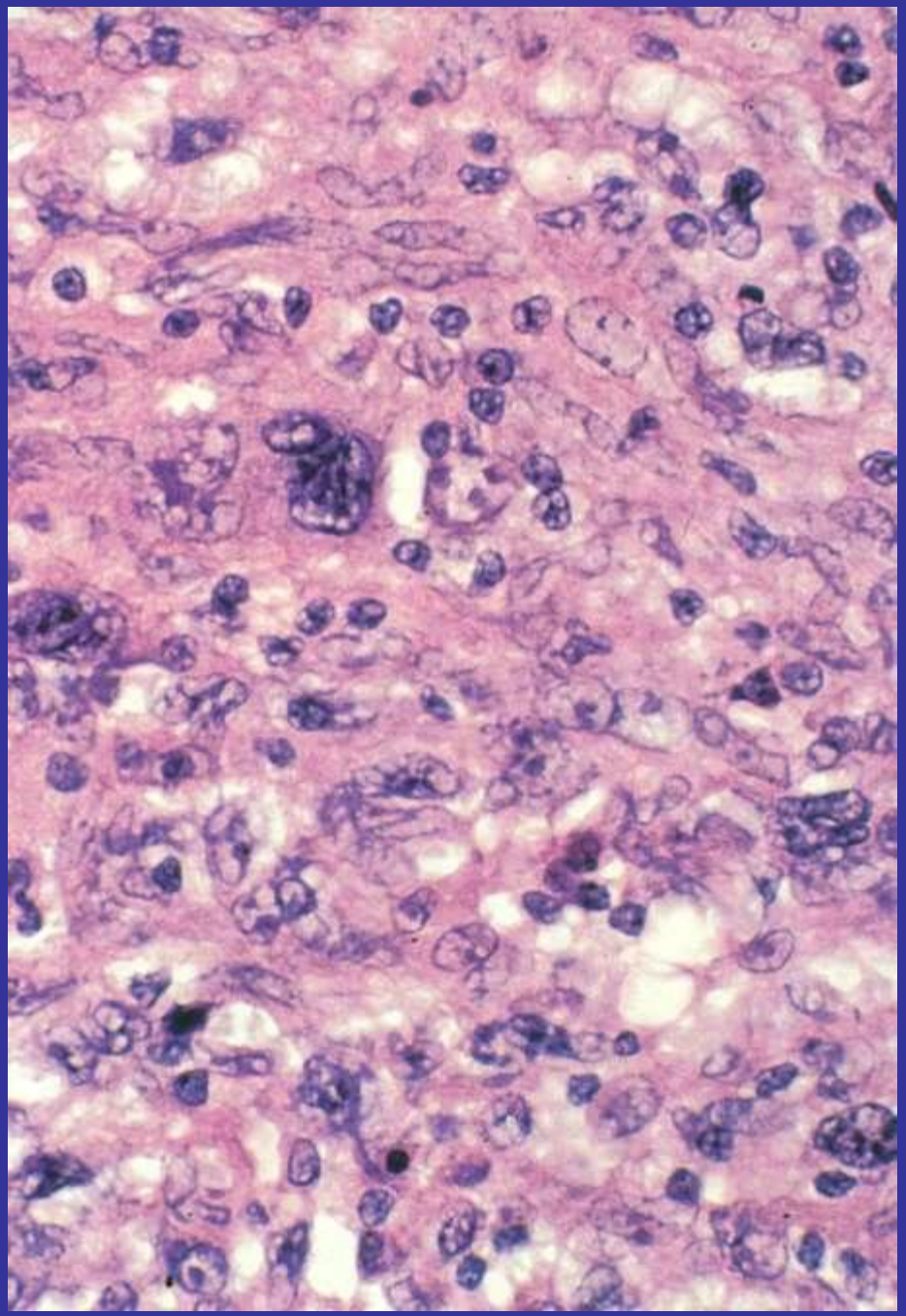
- Grade 2
  - Polymorphous lymphoid infiltrate
  - 5-20 EBV-positive cells/HPF
  - Necrosis more commonly seen

# Grading

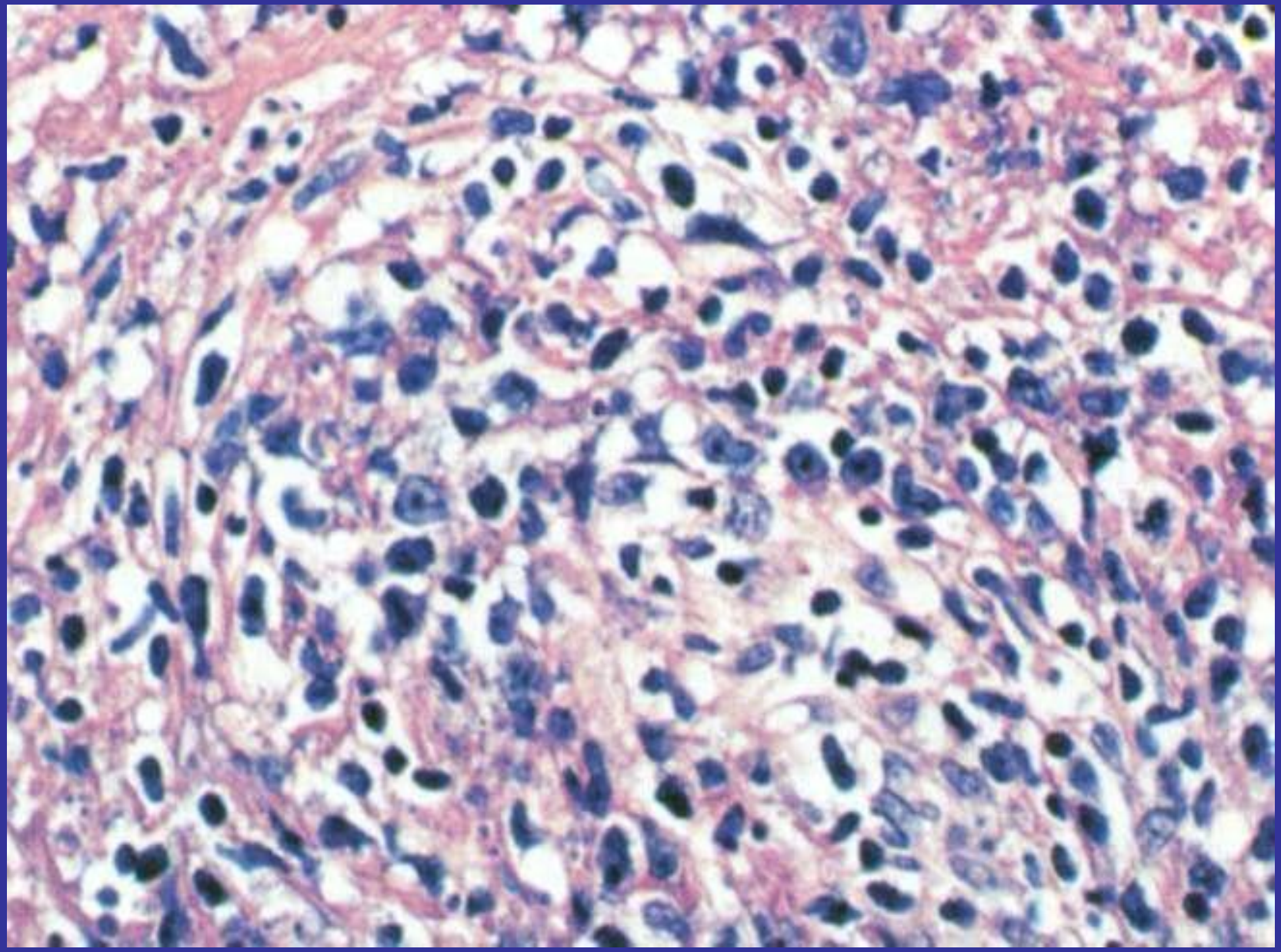
- Grade 3
  - Readily identified as malignant lymphoma on histology
  - Numerous large lymphoid cells (but inflammatory background is still present)
  - Numerous EBV-positive cells (>20/HPF)
  - Markedly pleomorphic and Hodgkin-like cells are often present
  - Necrosis is usually extensive

# Grading

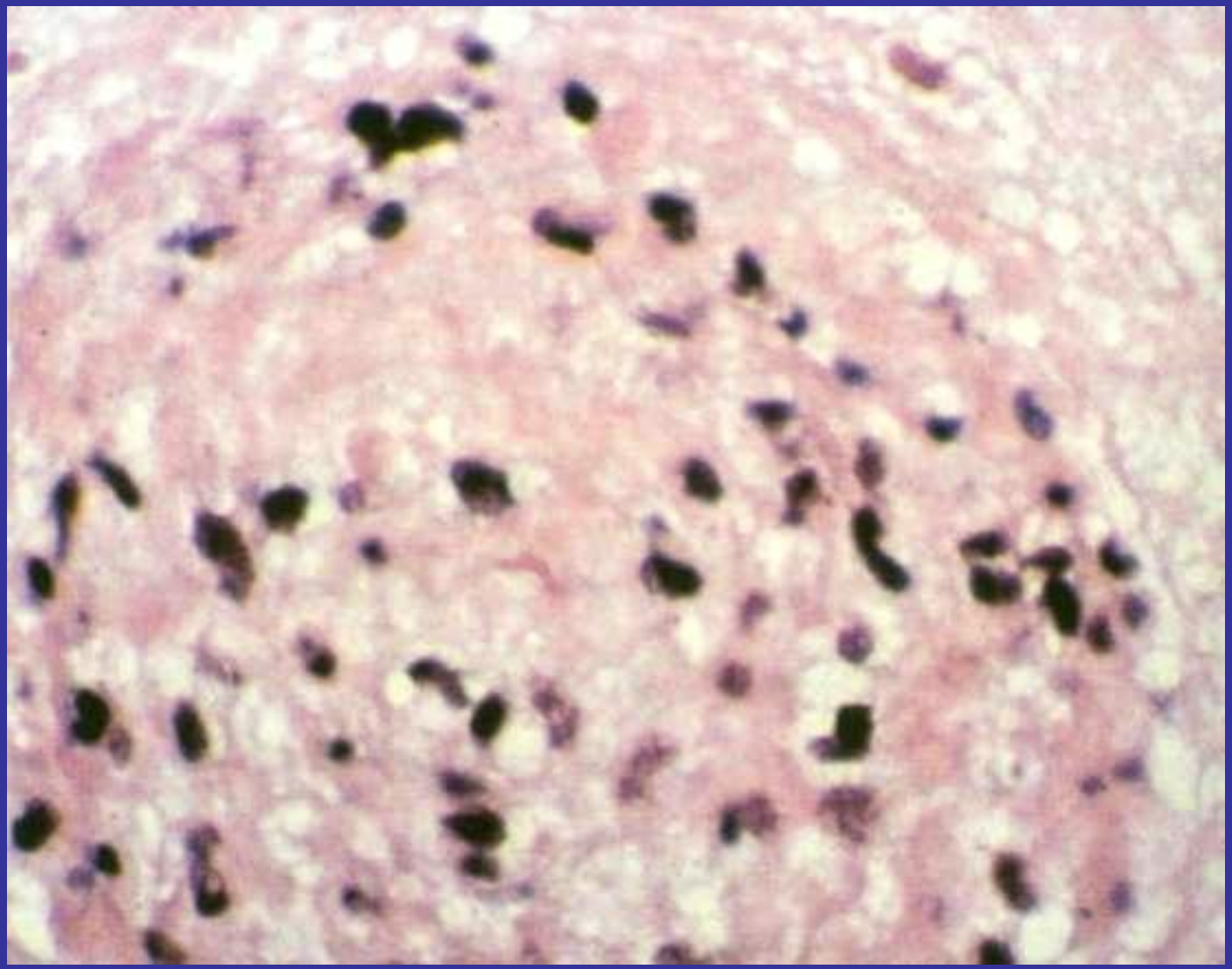
- Grade 3 lesions
  - Subtype of DLBCL
  - However, some cases may spontaneously regress



Grade 3



Grade 3



Grade 3 – positive for EBV with *in situ* probe

# Immunophenotype

- EBV positive
- LMP1 usually positive in larger atypical cells
- CD20 positive
- CD79a and CD30 variably positive
- CD15 negative
- Monoclonal cytoplasmic Ig expression only rarely seen

# Immunophenotype

Background reactive T-lymphocytes

- CD3 positive
- CD4-positive

CD8-positive cells very few in number

# Genetics

- Most Grade 2 or 3 disease
  - Clonal Ig genes
  - Different clones may be identified in different anatomic sites
- Grade 1 disease
  - Demonstration of clonality is inconsistent
    - Rare EBV-positive cells, or
    - polyclonal

# Differential Diagnosis

Natural Killer/T-cell lymphoma, Nasal Type

- EBV positive cells in higher number
- EBV positivity in cells positive for CD56 and cCD3ε
- Lungs are rarely involved

# Differential Diagnosis

Subcutaneous Panniculitis-Like T-cell Lymphoma

- Monomorphic infiltrate
- Cytotoxic T-cells rimming fat spaces or invading vessels
- More CD8 positive T-cells
- EBV negative

# Prognosis

- Variable natural history
  - Median survival <2 years in most patients
  - Waxing and waning with spontaneous remission in some patients
- Grade 1 and 2 disease may respond to Interferon 2b
- Grade 3 disease may respond to aggressive chemotherapy
- Most common cause of death is progressive pulmonary disease