Post Liver Transplant Infections

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Infections in Liver Allograft Recipients

Common

- 60-80% of patients have at least one episode of infection
  - bacterial 50-60%, viral 20-40%, fungal 5-15%, other <10%
- Prevalence as a cause of death seems to be declining
  - > 50% before 1980, now < 10%

Broad spectrum of organisms and clinical manifestations

Predisposing factors	Time of onset	Examples/comments
Major abdominal surgery	First month	Bacterial/fungal wound infection
Persistent/recurrent infection in recipient	Immediate	Hepatitis viruses (A,B,C,D, E, G)
Immunosuppression	1-6 months	Opportunistic viruses, fungi, protozoa
Other transplant complications	Variable	Bacterial/fungal infection complicating ischaemic bile duct necrosis

Most infections diagnosed by non-histological methods & don't involve liver

Viral Infections in the Liver Allograft

Opportunistic Infections

- Systemic infections - liver variably involved
  - Primary infection (no previous exposure)
    - More severe, commoner in children
  - Re-activation as a consequence of immunosuppression
- Mainly occur during first few months of transplantation

Hepatotropic Viruses

- Liver primary site of infection
  - Persistence/recurrence of infection in the recipient
  - Acquired from other sources (e.g. donor, blood products, other)
- Liver disease presents at any time following transplantation
  - Late post-transplant biopsies increasingly obtained in local hospitals

Opportunistic Viral Infections in the Liver Allograft

Cytomegalovirus	Commonest example in post-transplant biopsies
Epstein- Barr virus	Association with PTLD
Adenovirus	Liver involvement usually part of overwhelming infection (mainly seen at autopsy)
Herpes simplex virus	
Varicella zoster	
Human herpes viruses HHV-6, HHV-7	May interact with other complications (e.g. HHV-6 – rejection & HCV, HHV-7 – CMV hepatitis) • HHV-6 can cause mild hepatitis • one case of HHV-6 giant cell hepatitis (Potenza 2008)

CMV Infection in Liver Allografts – Changing Pattern of Presentatation

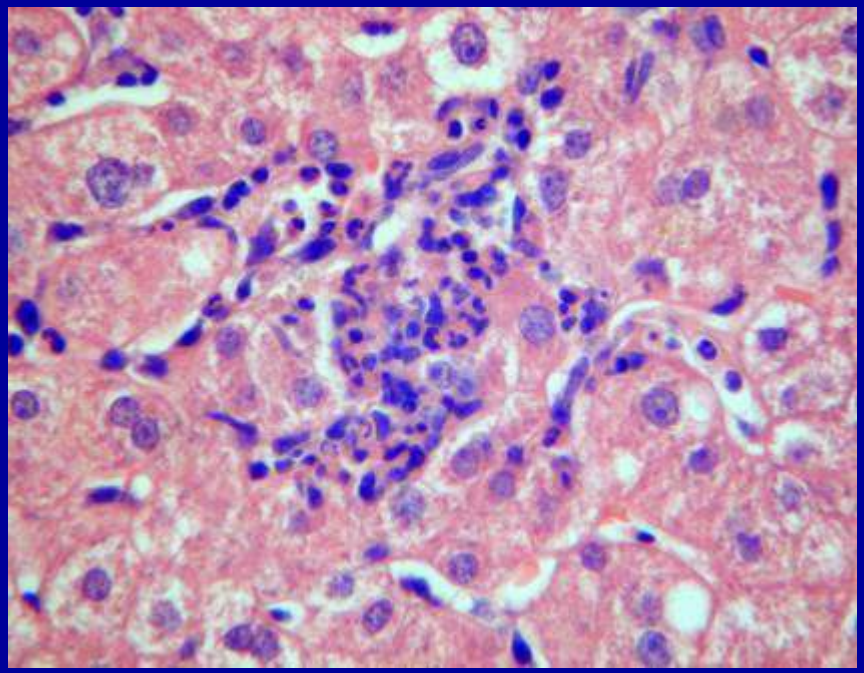
1980s/early 1990s

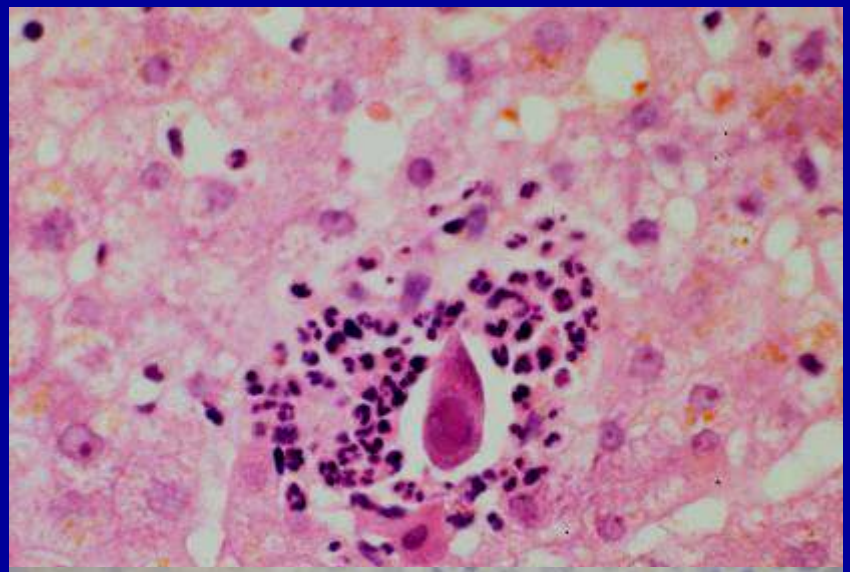
- CMV infection common (30-50%), frequently symptomatic (up to 25%) and associated with significant morbidity and mortality
- CMV hepatitis commonest manifestation of symptomatic CMV disease

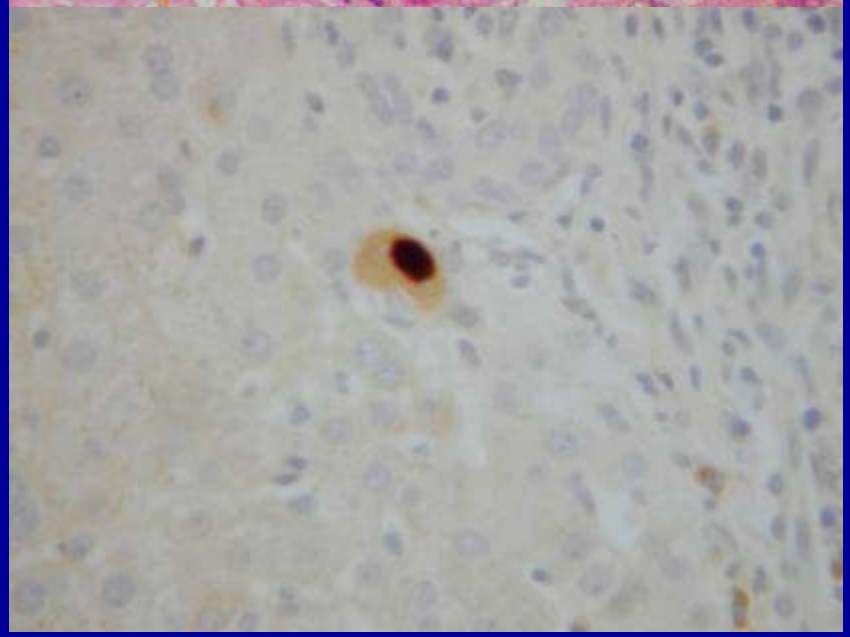
Late 1990s - current

- Use of prophylactic anti-viral therapy during first few months for “high risk” patients (donor seropositive/ recipient seronegative)
- Decline in overall prevalence of CMV infection and symptomatic disease (CMV hepatitis in $\leq$ 2% of patients)
- Late presentation after discontinuing anti-viral therapy
  - Generally mild disease
  - May still be associated with decreased graft or patient survival

CMV Hepatitis







Microabscess

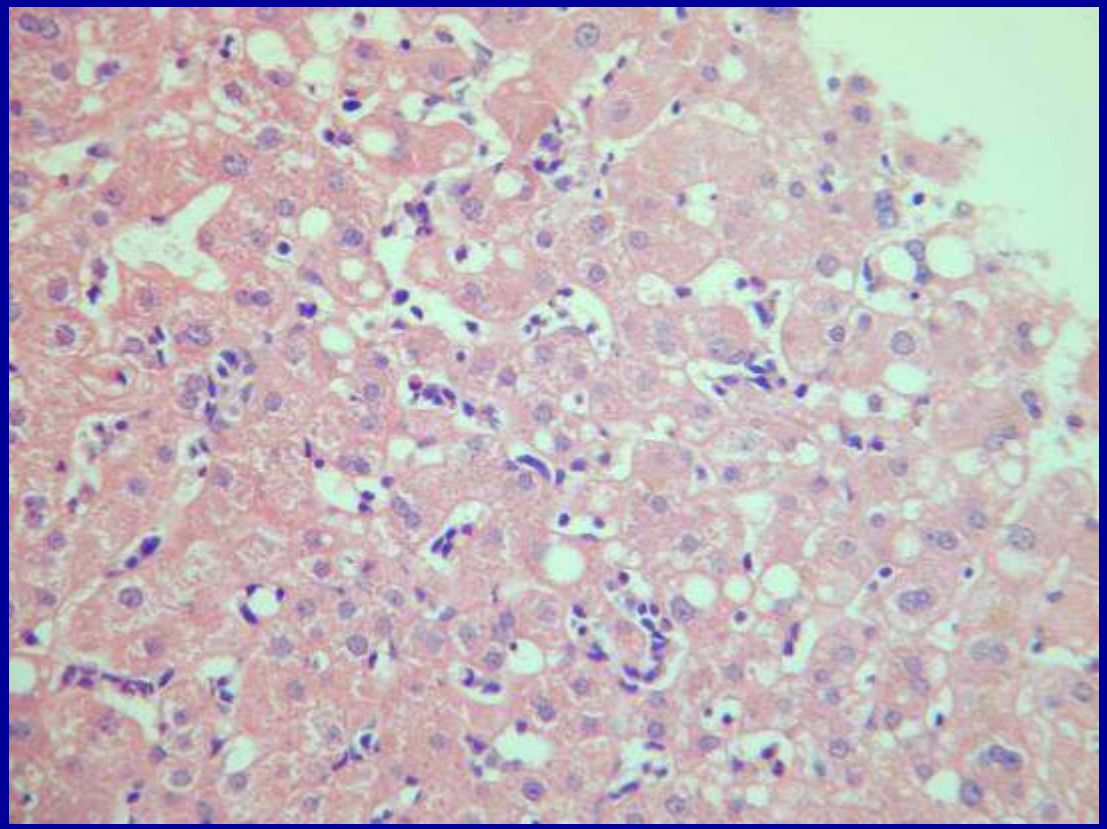
Also seen in:

- Other infections – bacterial/viral/fungal
- Biliary obstruction/cholangitis
- Graft ischaemia

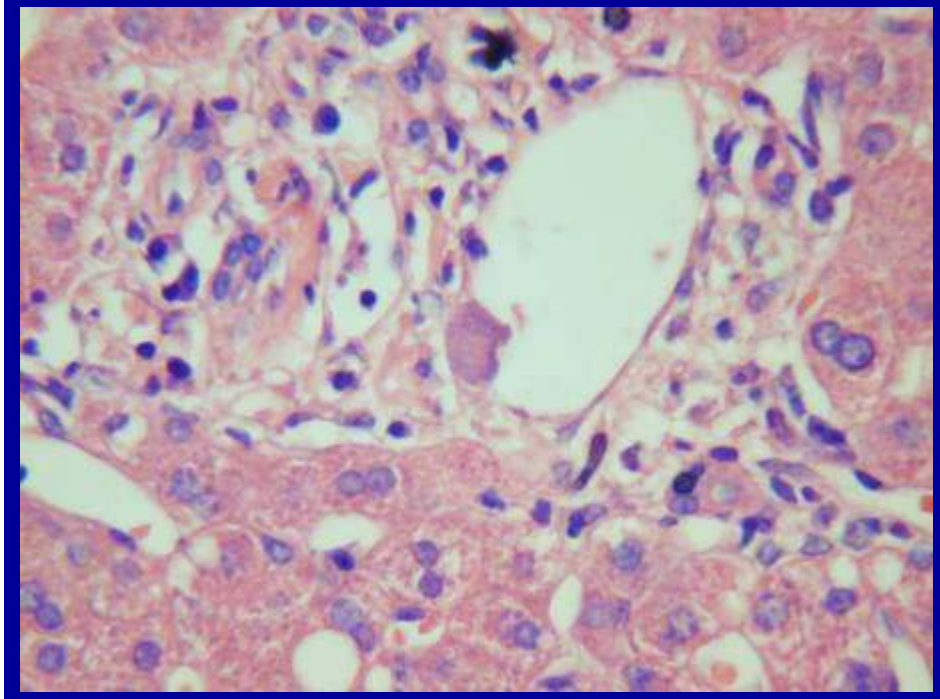
CMV Hepatitis

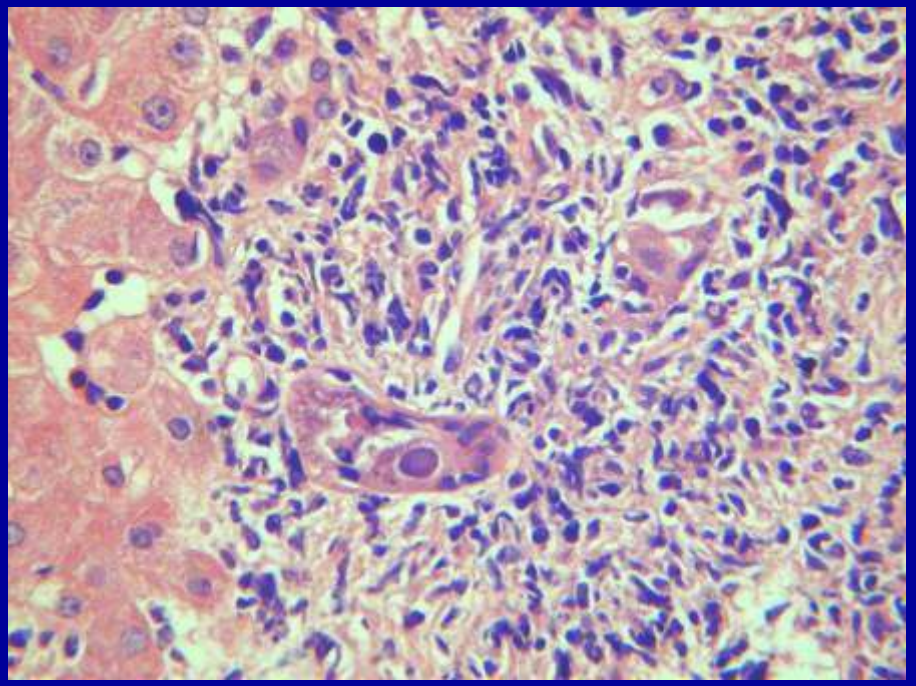
Other Patterns of Injury

- Lobular microgranulomas
- Diffuse spotty inflammation
- Sinusoidal lymphocytosis (EBV-like)



CMV Inclusions in Endothelial Cells and Bile Ducts





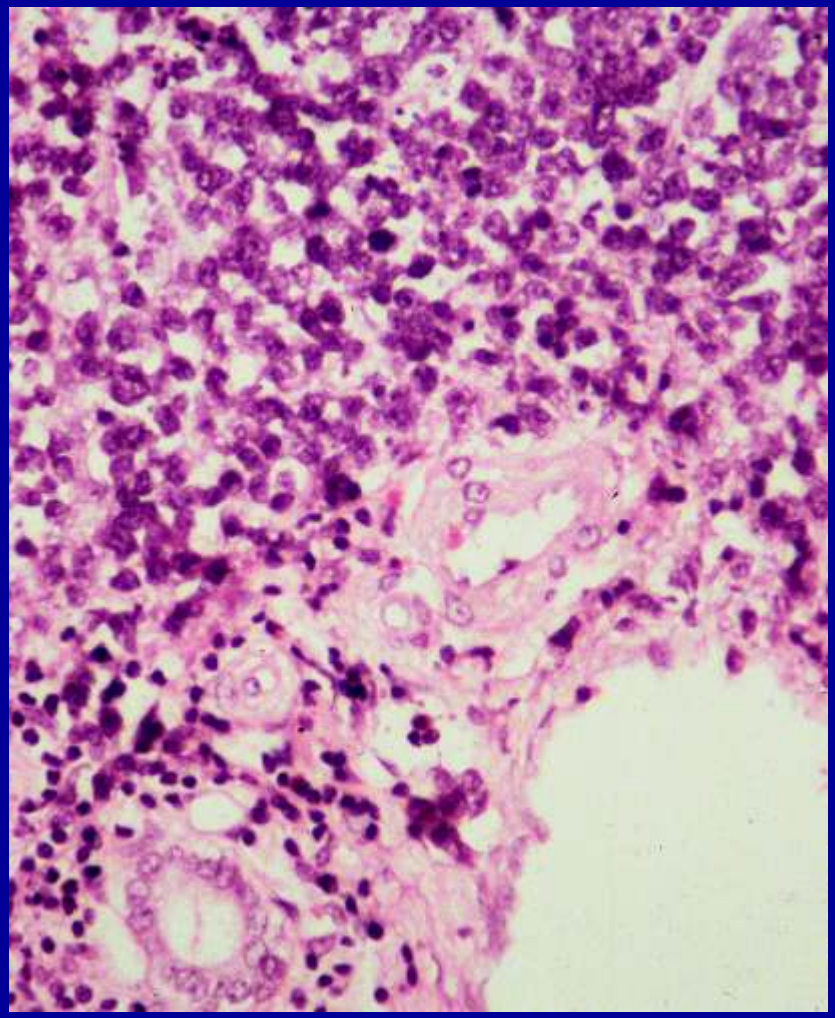
CMV and Rejection – Cause or Effect?

- Treatment for rejection predisposes to opportunistic infections
- CMV infects target cells of immune-mediated damage and stimulates immune responses (e.g. TNF-α, IFN-α release) which may augment rejection

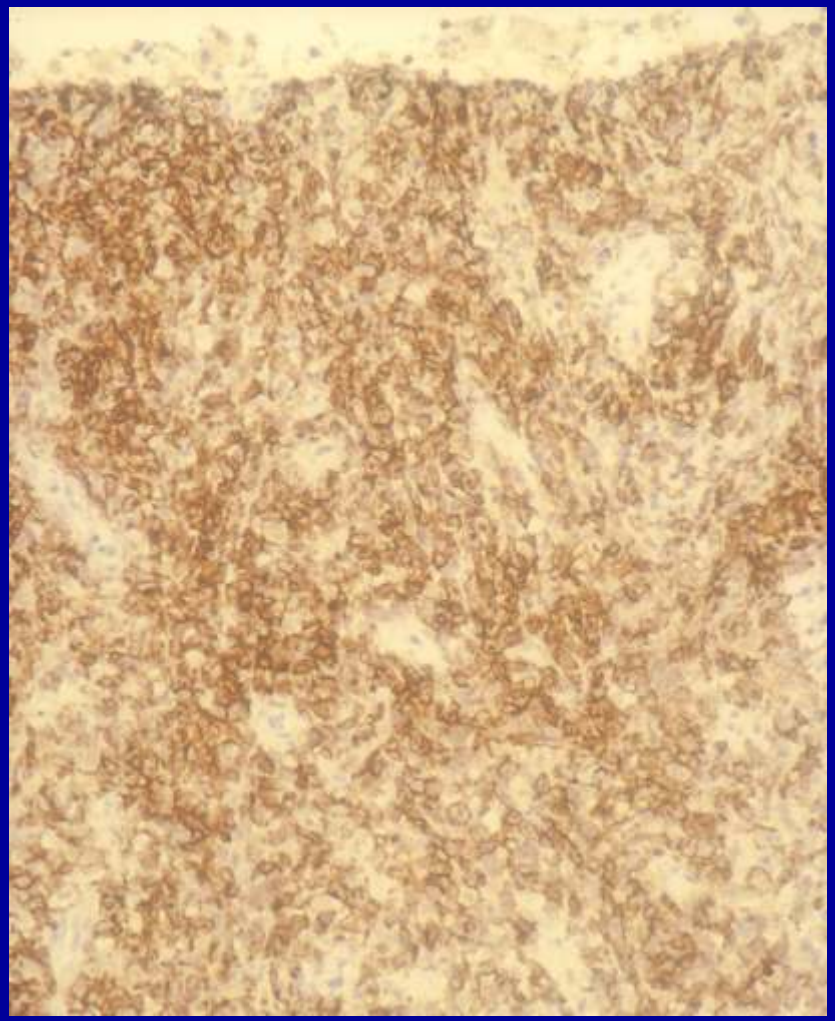
Epstein Barr Virus

- EBV infection universal by adulthood. Virus infects B lymphocytes. Remains in a latent phase, controlled by EBV-specific T cell response
- Immunosuppressive drugs interfere with T cell function & enable uncontrolled proliferation of EBV-infected B cells
- **Clinical manifestations:**
  - Most cases of re-activation asymptomatic
  - EBV hepatitis (resembles EBV hepatitis in native liver)
  - Post-transplant lymphoproliferative diseases (PTLD) (1-10% of patients)
    - Spectrum ranging from lymphoid hyperplasia to high grade lymphoma
    - Hepatic involvement common (particularly in donor-derived cases)
      - Solid masses, often near hilum (particularly in donor-derived cases)
      - Diffuse infiltrates, predominantly portal in location (may be difficult to distinguish from other causes of portal inflammation e.g. rejection)

EBV-associated PTLD – Portal Infiltration



Portal tract containing a
dense lymphoid infiltrate

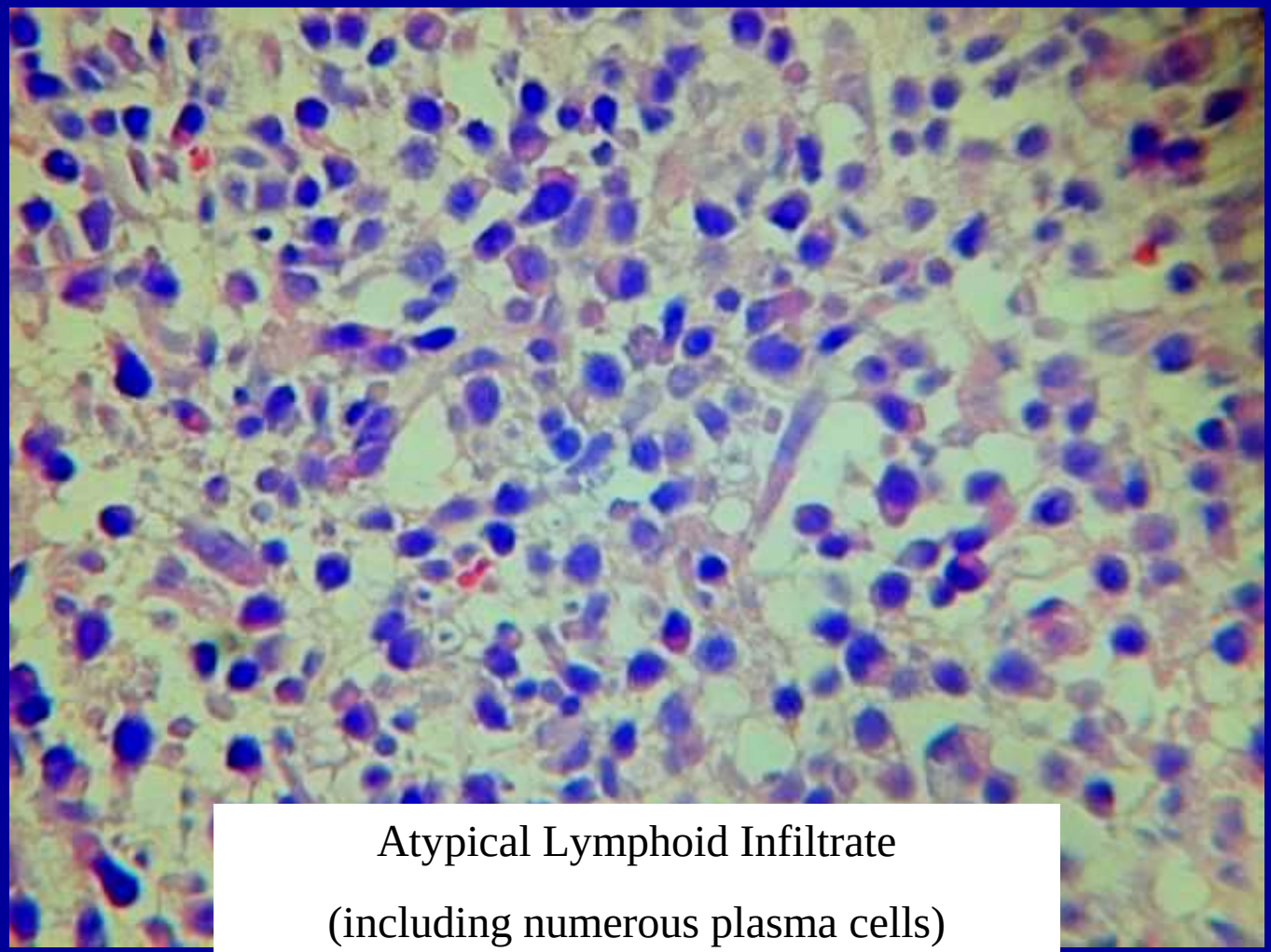


Pure population of B cells
(CD20 positive)

EBV-associated PTLD – solid masses

45 year old man –4 months post-transplant for PSC

Multiple liver lesions, up to 9cm diameter



Atypical Lymphoid Infiltrate

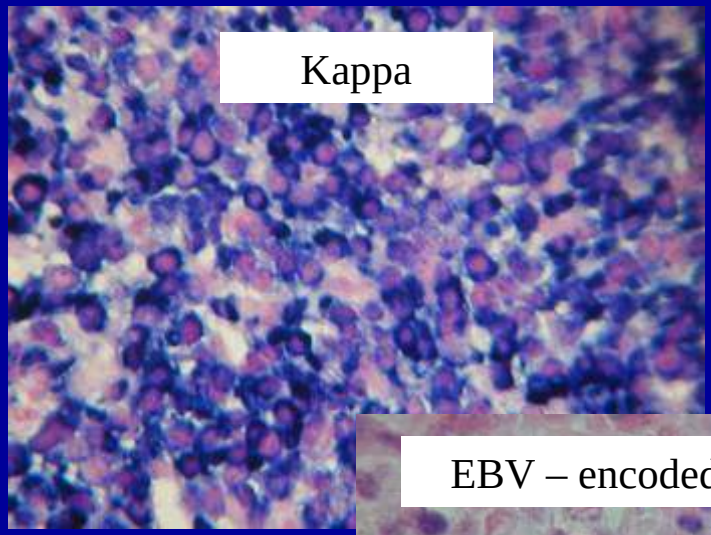
(including numerous plasma cells)

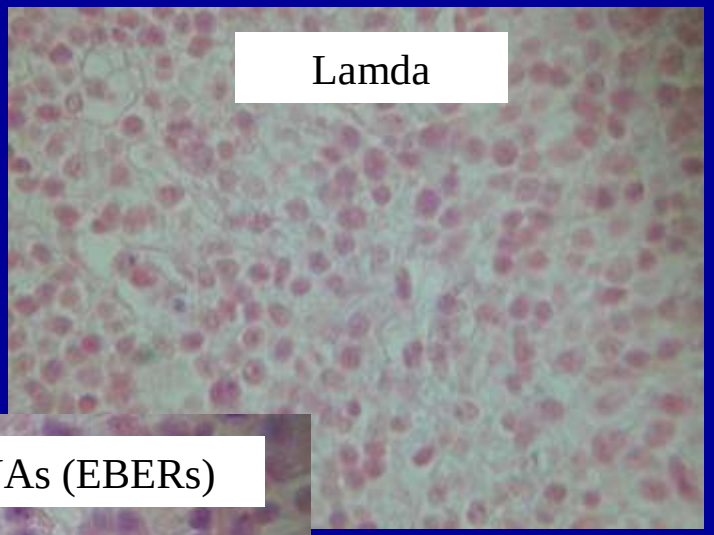
EBV-associated PTLD – solid masses

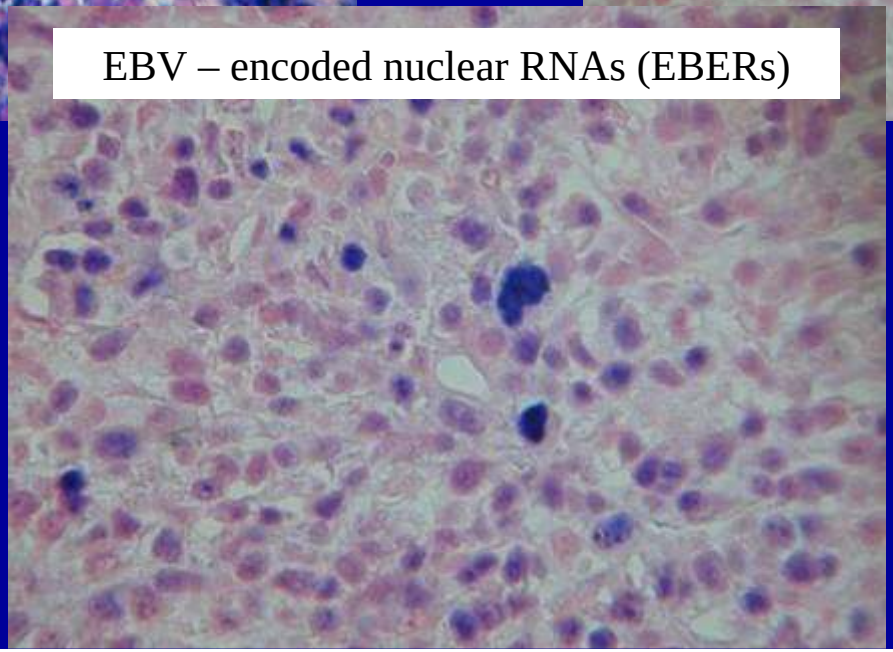
45 year old man –4 months post-transplant for PSC

Multiple liver lesions, up to 9cm diameter

In-situ Hybridization





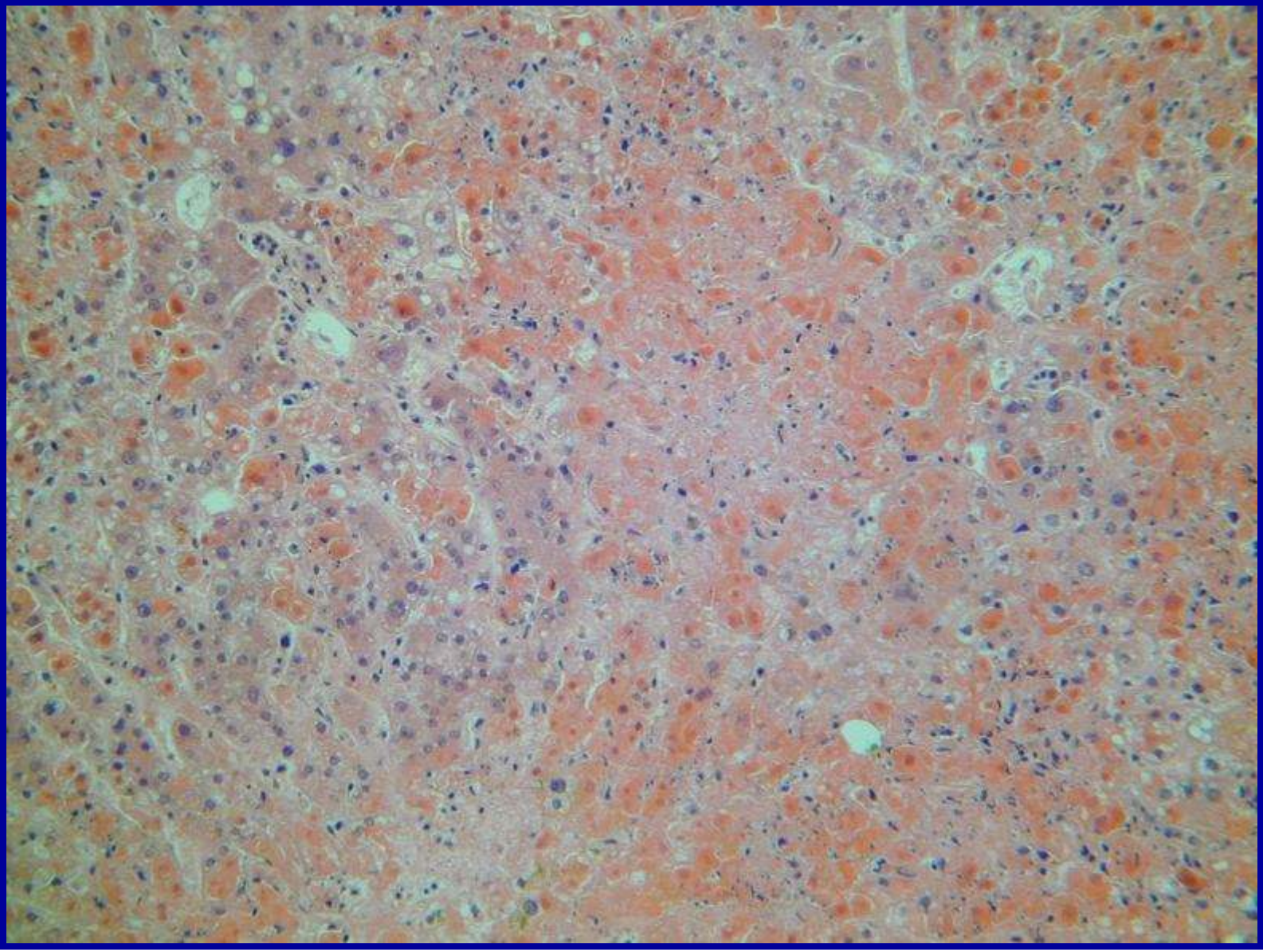


Adenovirus

- Mainly in children (primary infection)
- Symptomatic disease includes hepatitis, pneumonia, gastroenteritis
- Severe cases associated with extensive hepatic necrosis

Adenovirus Hepatitis

Female, age 47. Acute liver failure, 10 months following cardiac transplant



Adenovirus Hepatitis

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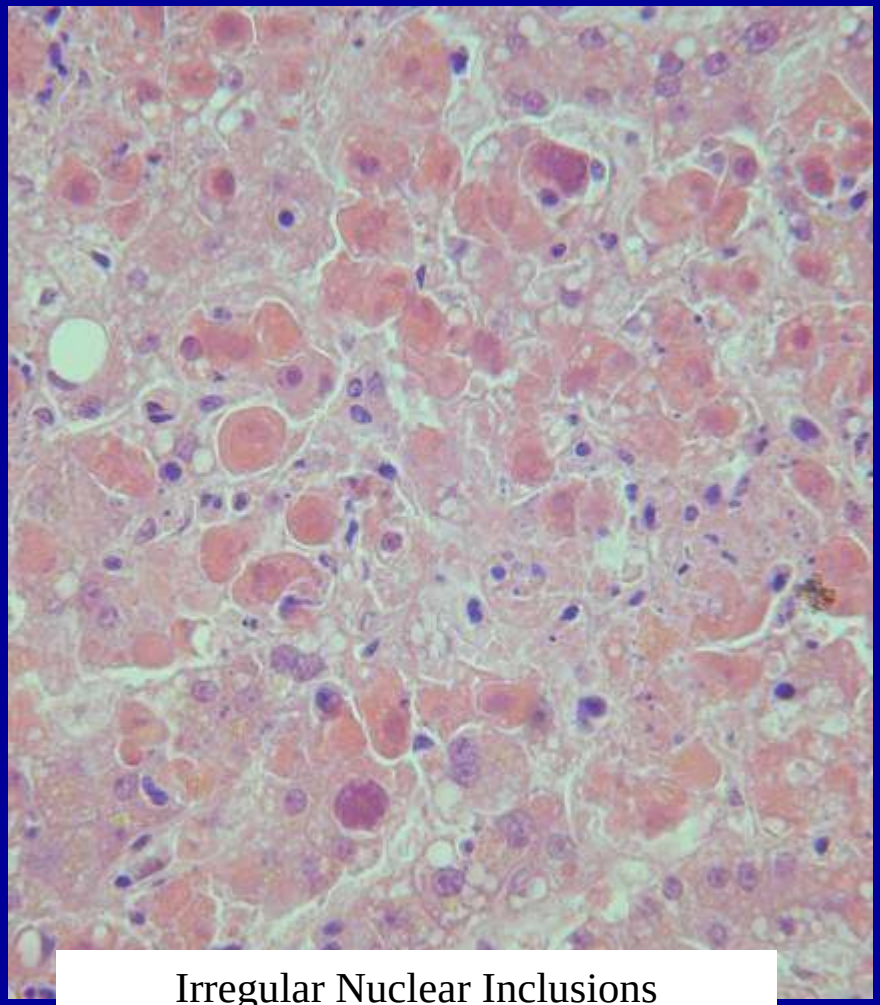
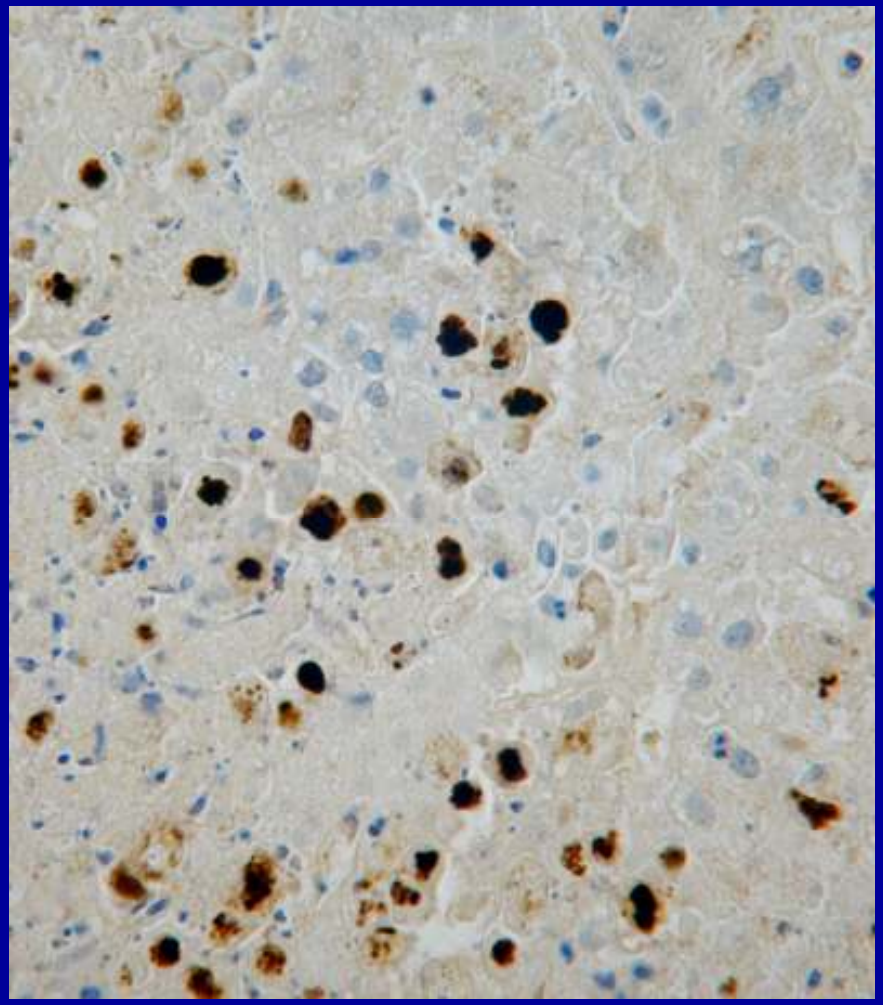
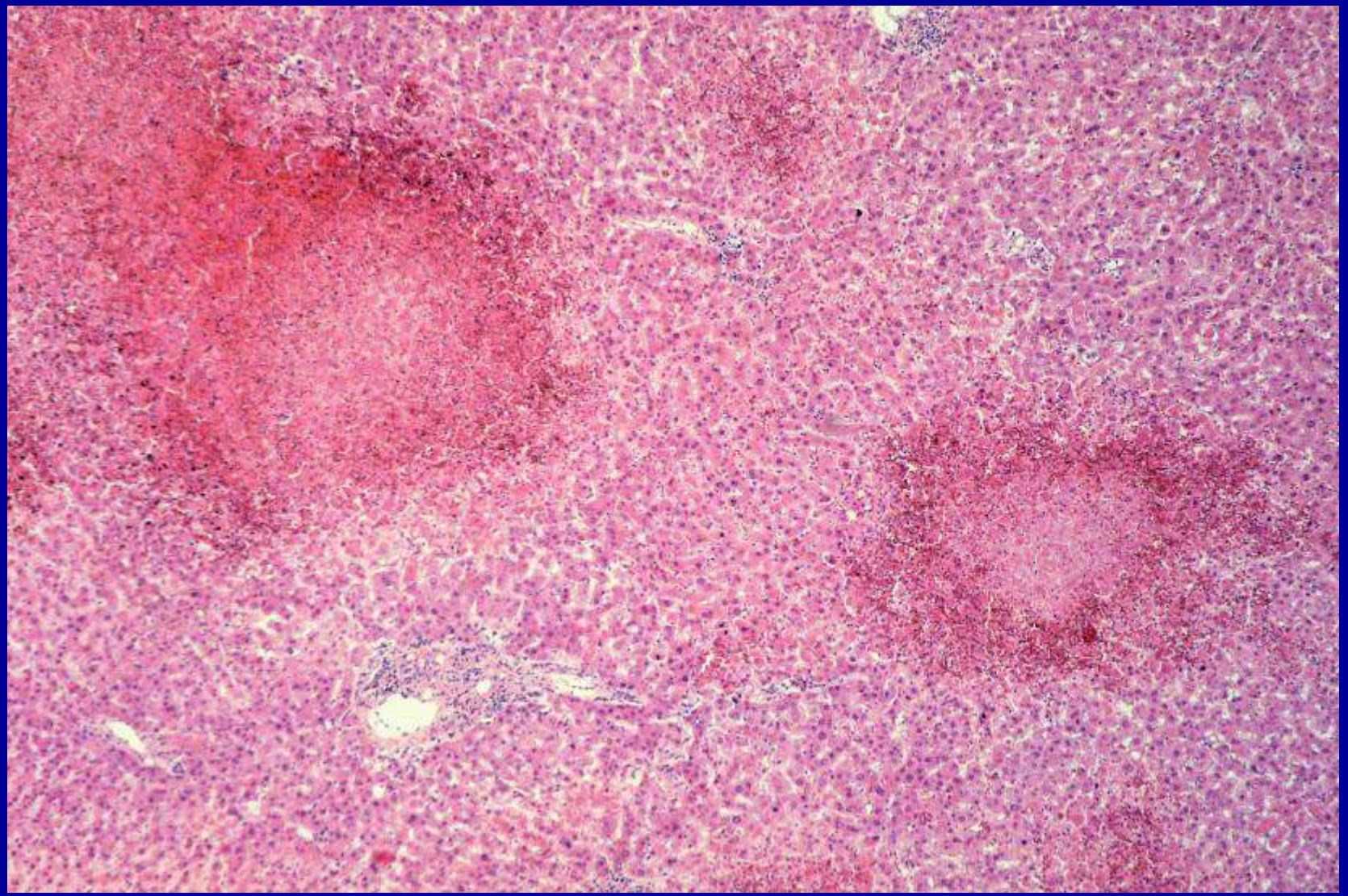


Irregular Nuclear Inclusions

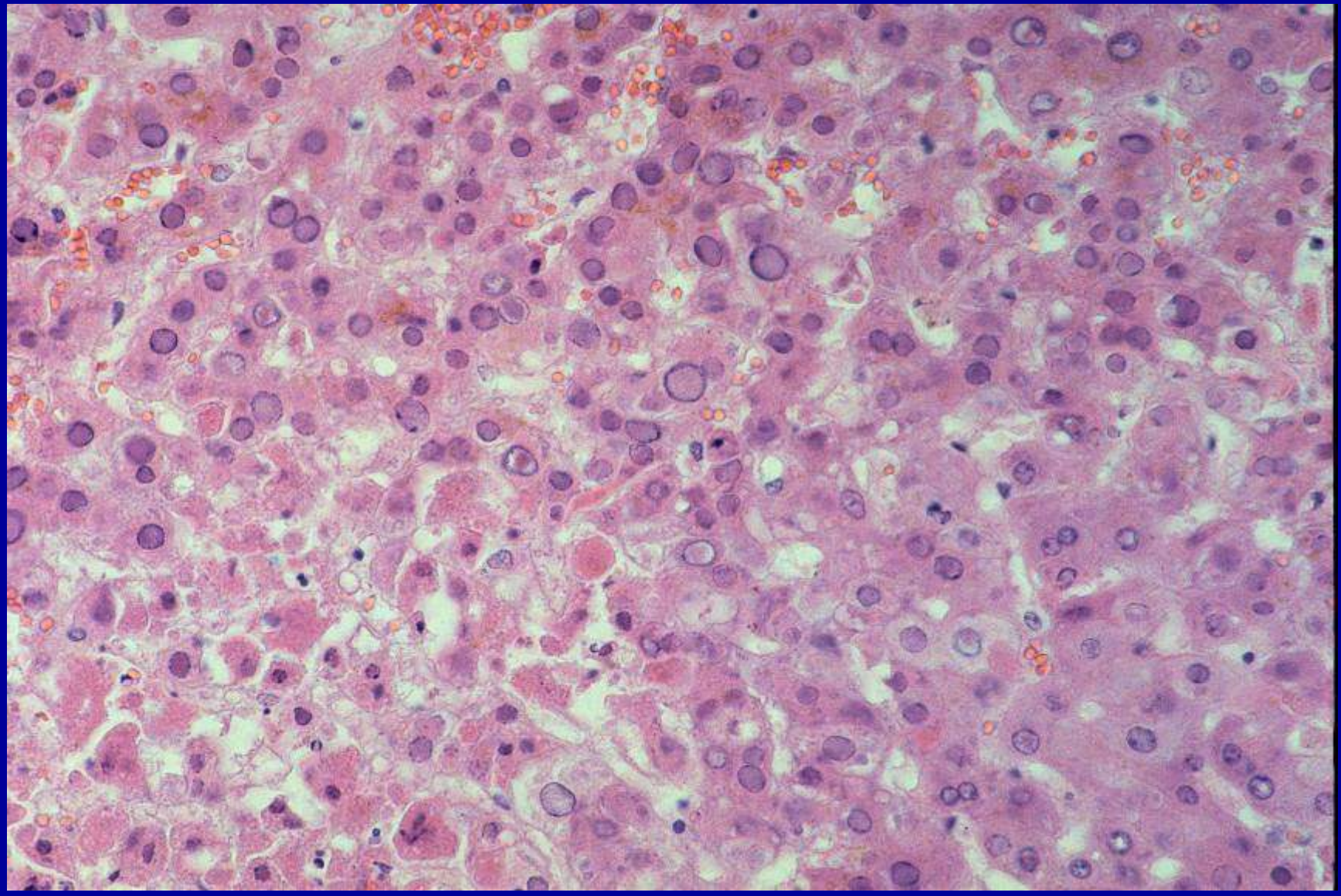
(“smudge cells”)



Herpes Simplex Hepatitis



Herpes Simplex Hepatitis



Hepatitis Viruses in the Liver Allograft

Hepatitis A	Occasional reports of acute hepatitis, possibly due to recurrent infection
Hepatitis B	Reduced incidence (and severity) • due to immunoprophylaxis and anti-viral therapy
Hepatitis C	Commonest indication for liver transplantation Recurrent disease major cause of graft dysfunction
Hepatitis D	Co-infection with HBV Less severe disease than HBV alone
Hepatitis E	May be associated with chronic hepatitis
Hepatitis G	Present in up to 60% of patients post-transplant (recurrent & acquired) No definite evidence for graft dysfunction

Recurrent Hepatitis B and C - Incidence and Clinical Impact

Hepatitis B

- Prevalence 15-85% (1980s – early 1990s) - reduced graft survival
- Anti-viral therapy (pre- and post-transplant)
  - greatly improved outlook (< 10% recur, generally mild and treatable)

Hepatitis C

- Commonest indication for transplantation in many centres
- Graft re-infection universal
  - begins within few hours of reperfusion
  - HCV-RNA >> pre-transplant levels
- Most cases (70-90%) result in graft inflammation
- Many progress to fibrosis/cirrhosis
  - Reduced graft survival

Hepatitis B and C in the Liver Allograft
Histological Features

Typical Histological Features

- as seen in the non-transplanted liver

Atypical Histological Features

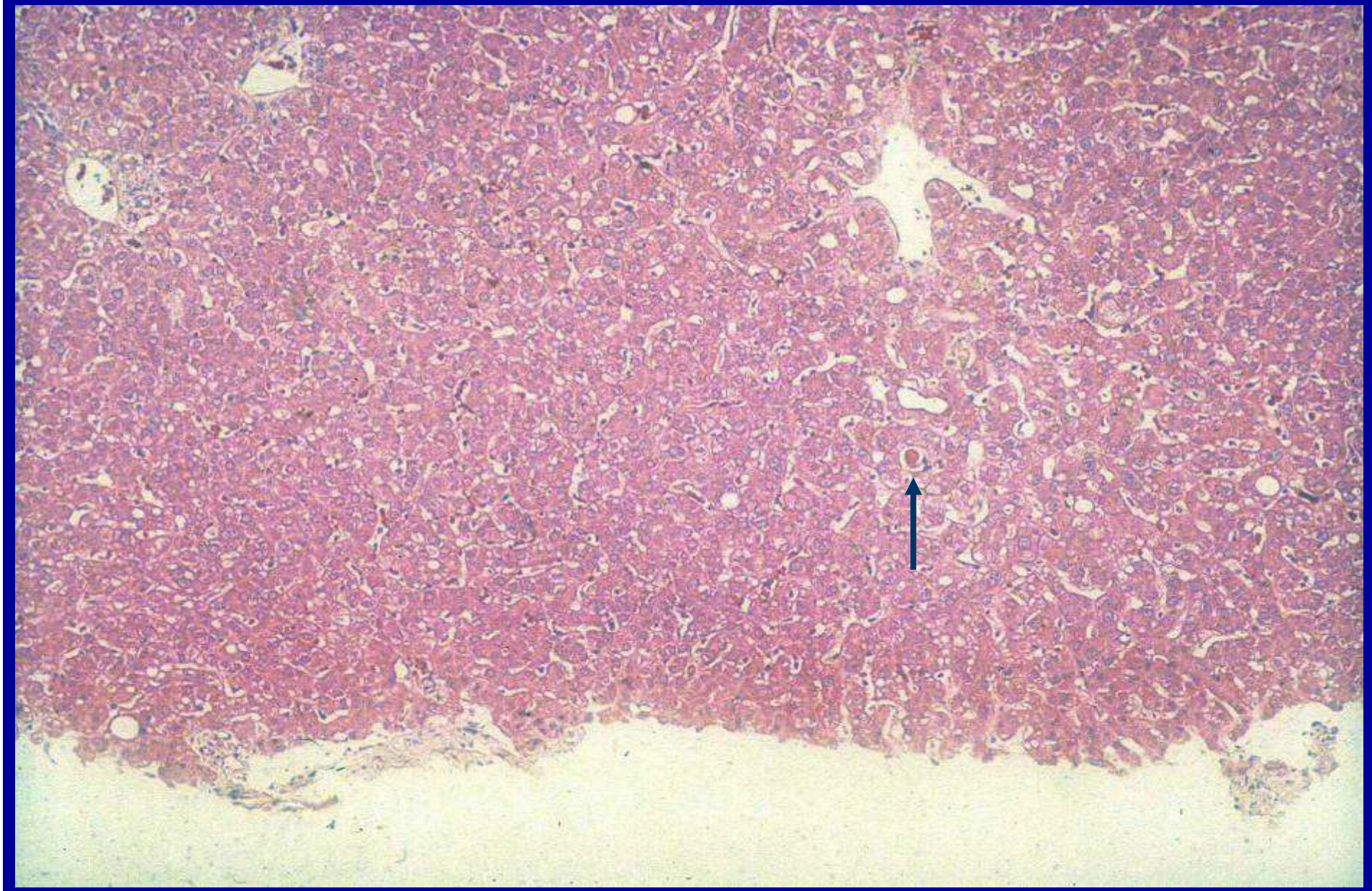
- modified by immunosuppression
- interaction with other complications

- Many post-transplant biopsies have features reflecting more than one process
- Liver biopsy may help to identify main cause of graft damage

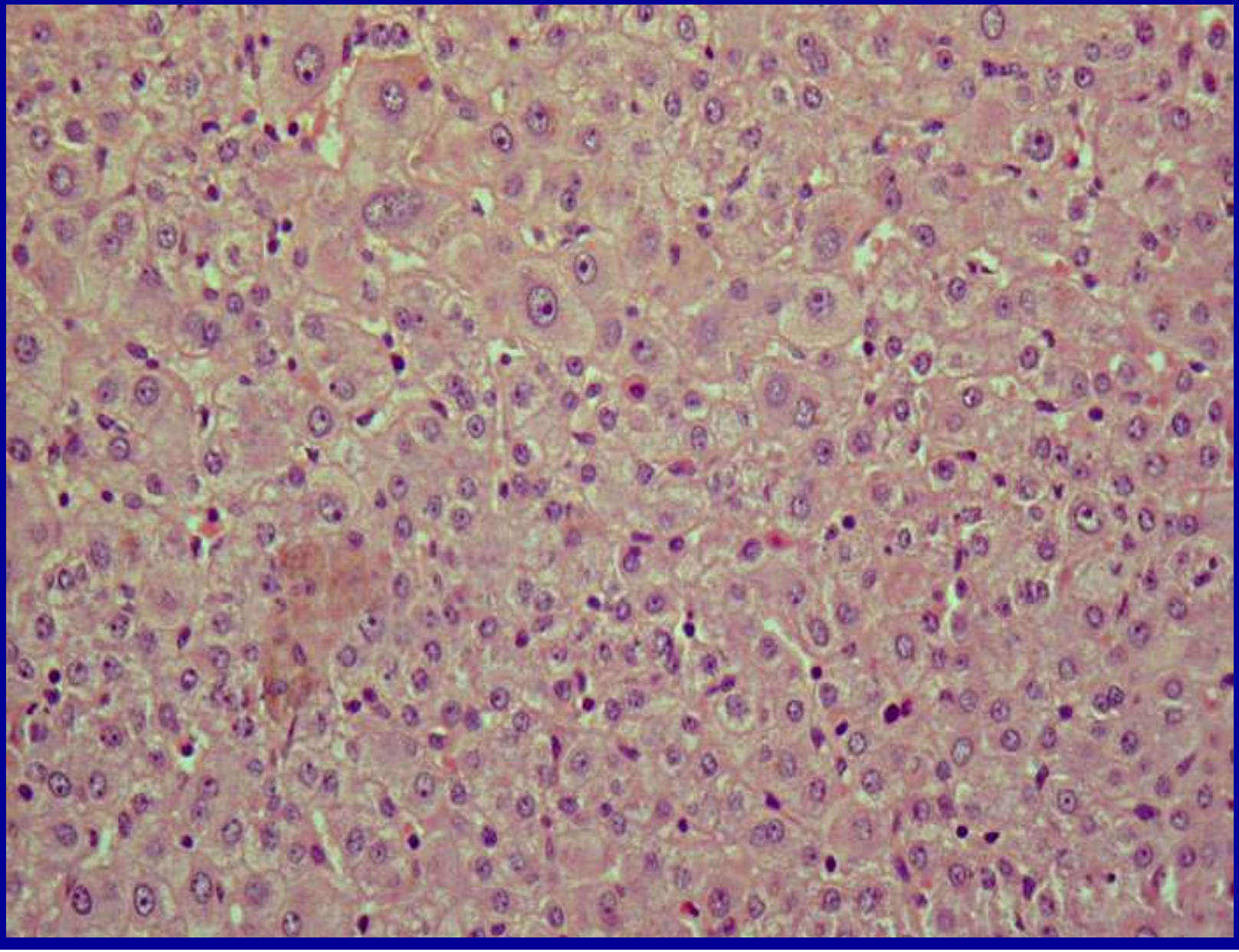
Hepatitis B & C in Liver Allografts
Evolution of Histological Changes

Phase (time post-transplant)	**Histology**	**Comments**
Early infection (0-2 months)	Mild non-specific changes	Lobular disarray Acidophil bodies Lack of inflammation Steatosis (in HCV) Positive staining for viral antigens
Established infection (2-4 months)	Acute hepatitis	Lobular inflammation (usually mild)
Progressive damage (> 6 months)	Chronic hepatitis	Portal/periportal inflammation Fibrosis/cirrhosis

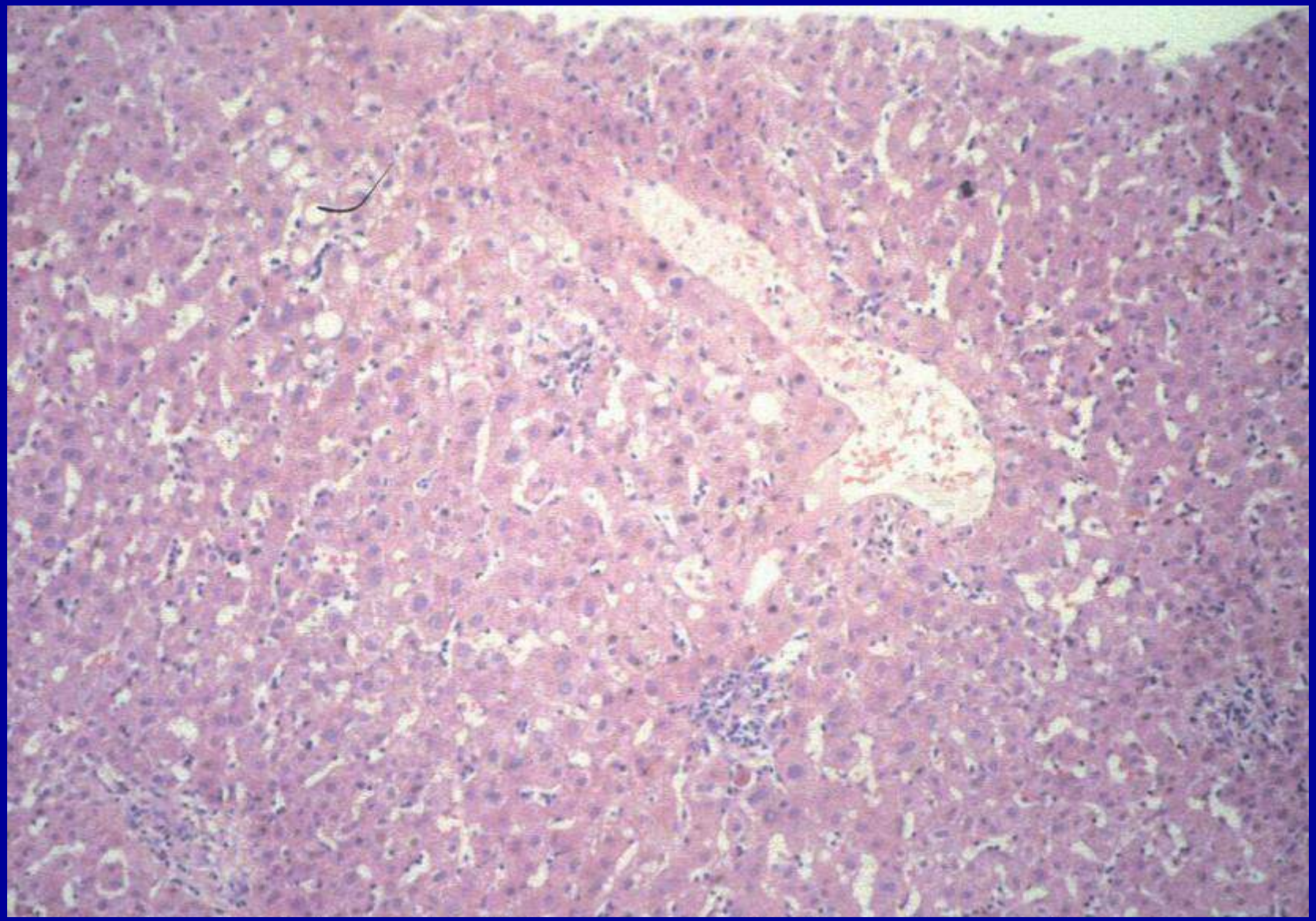
Recurrent HCV –5 weeks post-OLT



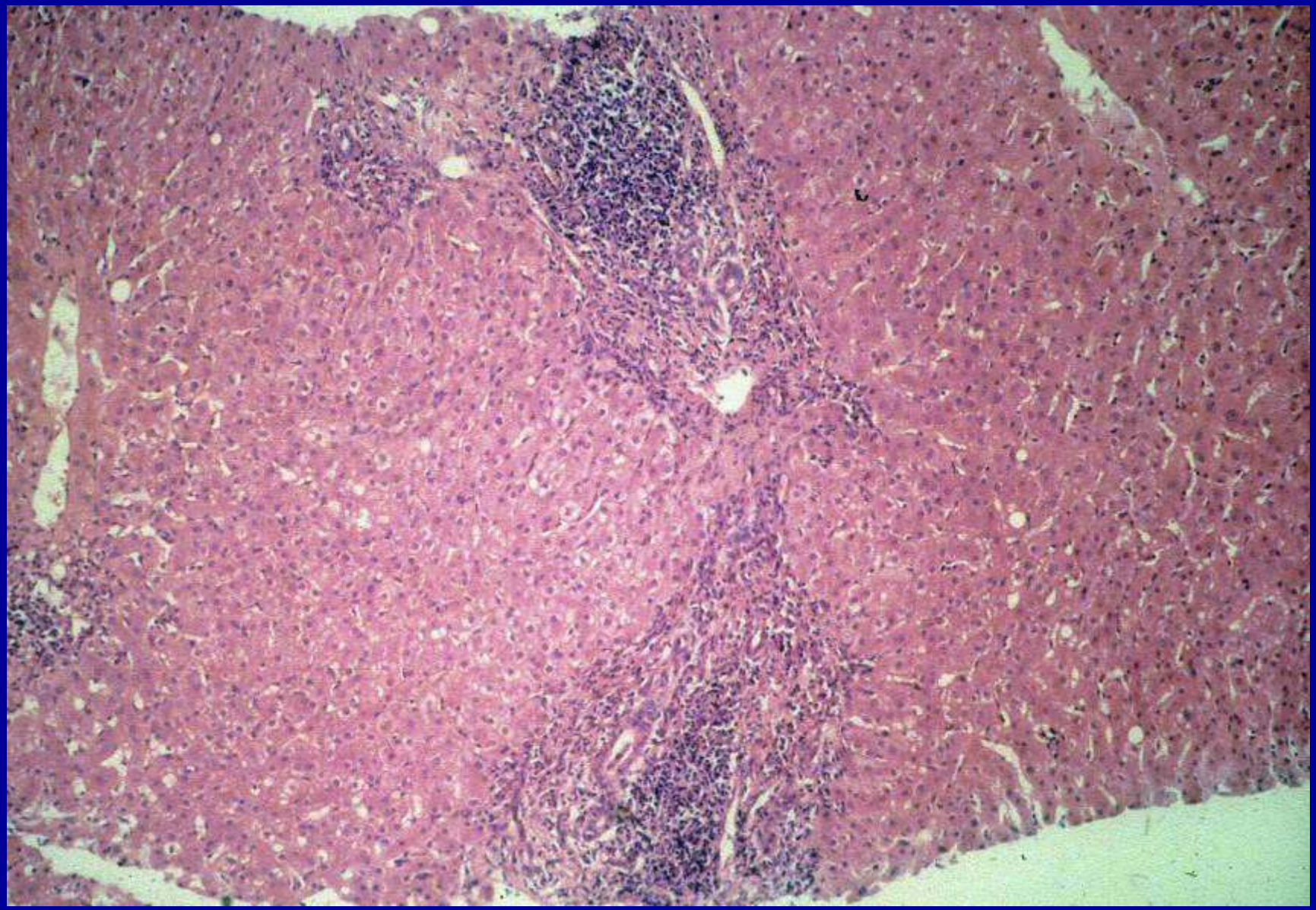
Early Recurrent HCV
lobular disarray, variation in cell size



Recurrent HCV – 3 months post-OLT
spotty lobular inflammation (mild)



Recurrent Hepatitis C – 6 months post-OLT
Chronic Hepatitis

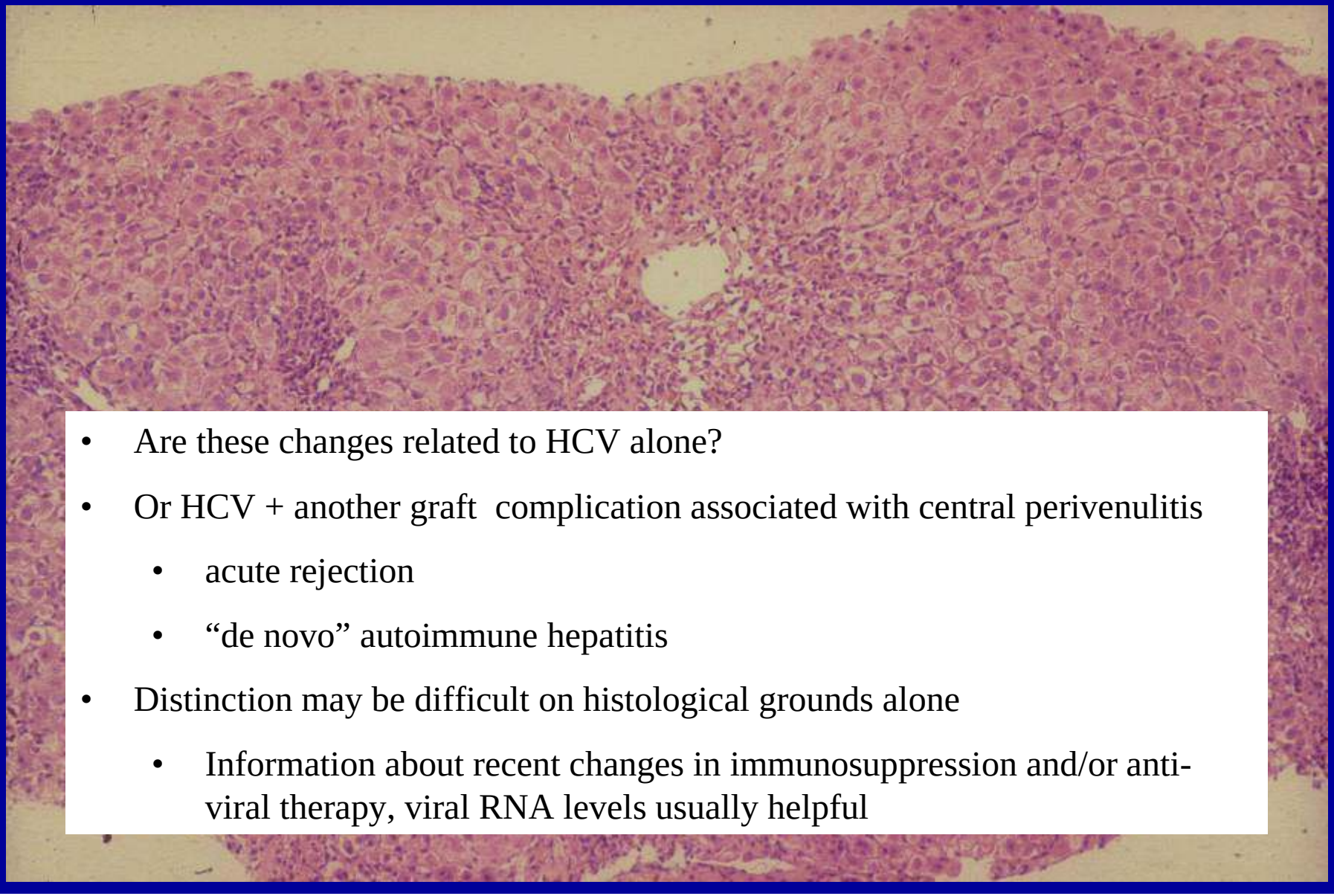


Hepatitis B & C in the Liver Allograft
Differences Compared with HBV/HCV in the Native Liver

- More aggressive disease
  - More severe inflammatory activity
  - More rapid progression to fibrosis and cirrhosis
    - e.g. 10-30% of HCV+ patients cirrhotic by 5 years, 50% by 10years
  - Cholestatic features (fibrosing cholestatic hepatitis)

- Hepatitis C
  - Interaction with rejection
  - Association with NAFLD
  - Hepatitis C with “autoimmune features” (? de novo AIH)

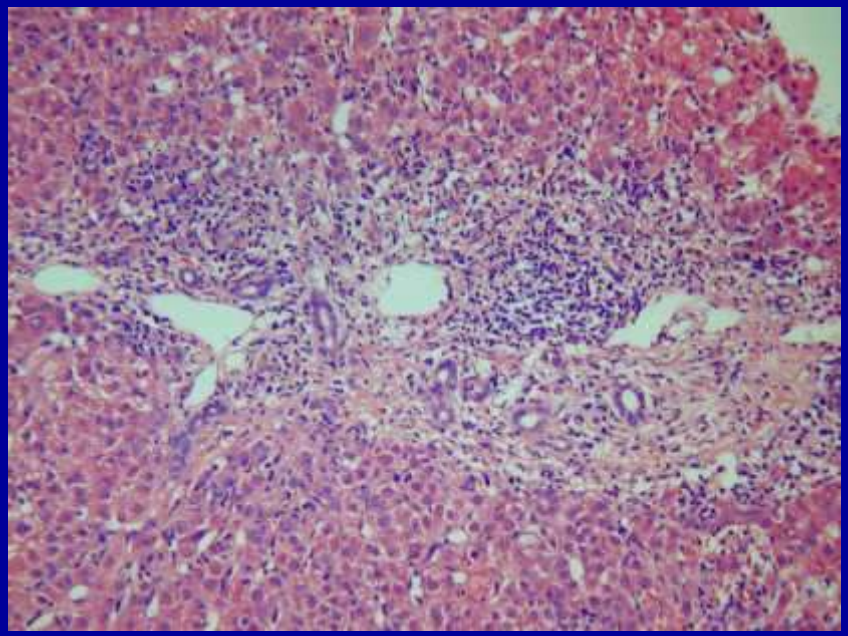
Recurrent Hepatitis C – 12 months post-transplant
prominent lobular inflammation with zone 3 necrosis (central perivenulitis)

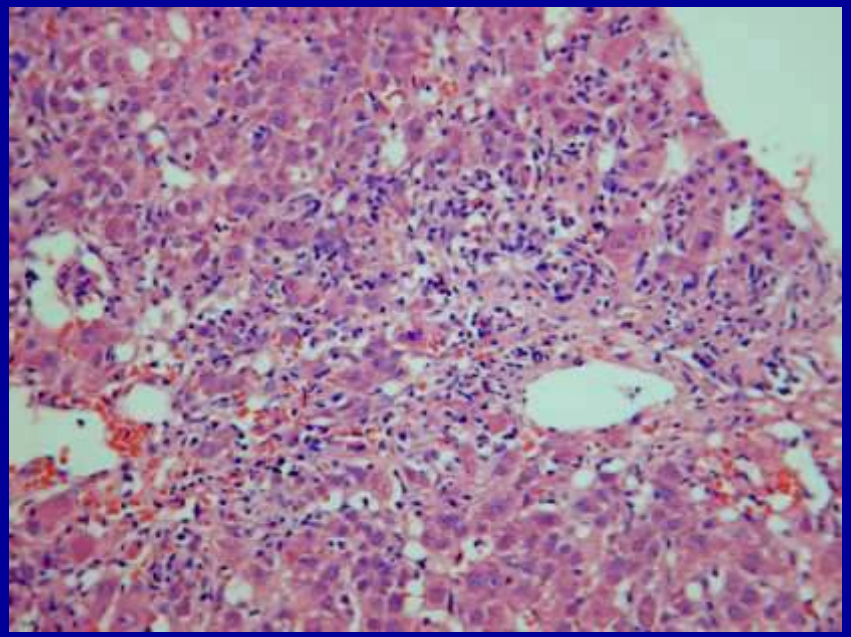


- Are these changes related to HCV alone?
- Or HCV + another graft complication associated with central perivenulitis
  - acute rejection
  - “de novo” autoimmune hepatitis
- Distinction may be difficult on histological grounds alone
  - Information about recent changes in immunosuppression and/or anti-viral therapy, viral RNA levels usually helpful

Aggressive Recurrent HCV

- Male, age 52. 21 months post-LT for HCV
- Antiviral therapy recently stopped because of nephric abscess
- Presented with acutely deranged LFTs (AST 650)
- Became HCV-RNA positive





Hepatitis B and C in Liver Allografts
Cholestatic Features ("Fibrosing Cholestatic Hepatitis")

- High viral levels
- Most cases present within first 12 months post-transplant
- Hepatocellular injury with little/no inflammation (viral –induced cytopathy)
- Poor prognosis (rapidly progressive graft failure)

HBV

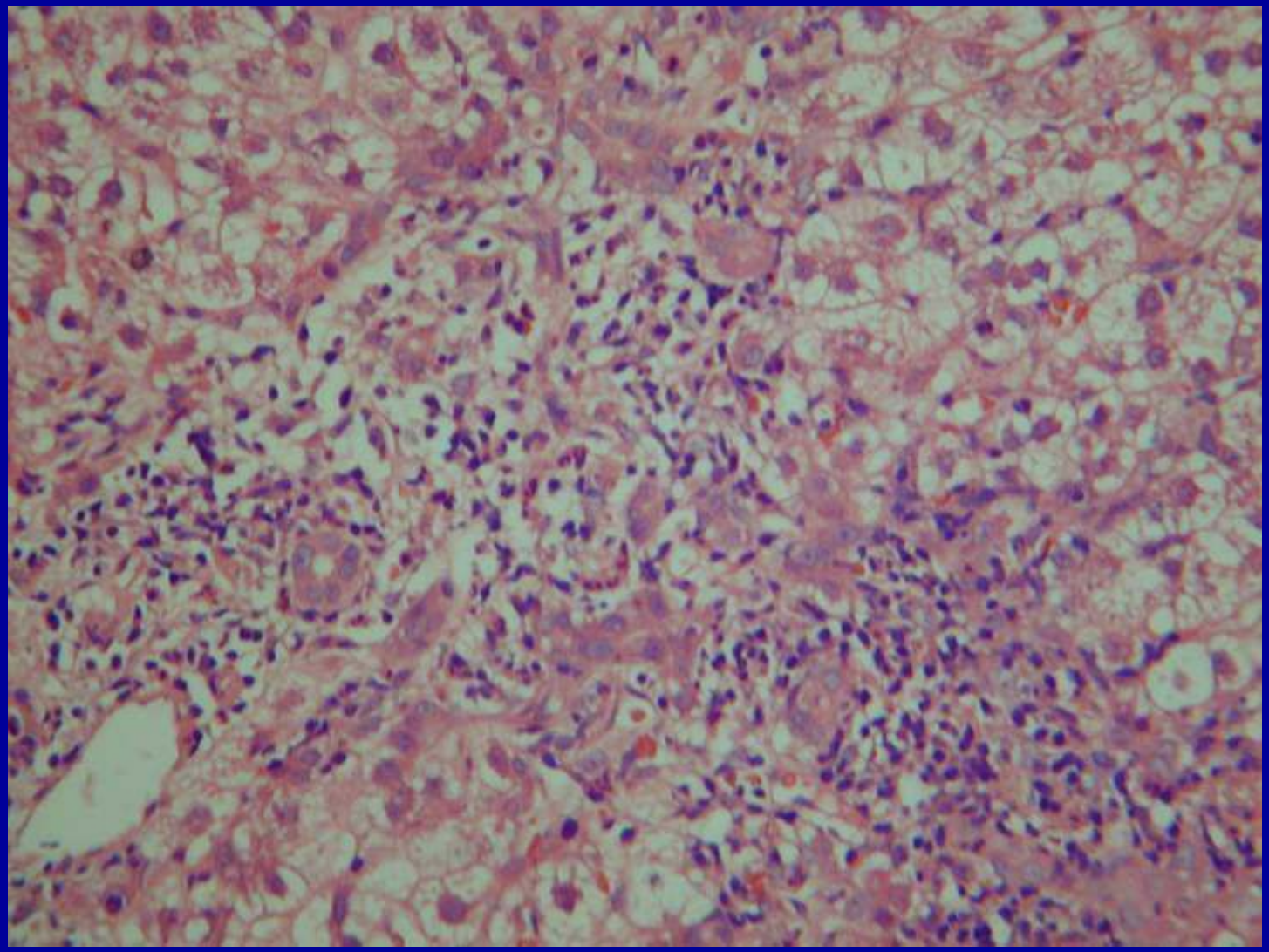
- FCH rarely seen now due to effective anti-viral therapy

HCV

- Cholestatic features frequently co-exist with more typical hepatitic changes
- Outcome variable – some cases respond to reduction in immunosuppression +/- anti-viral therapy

Cholestatic Hepatitis C

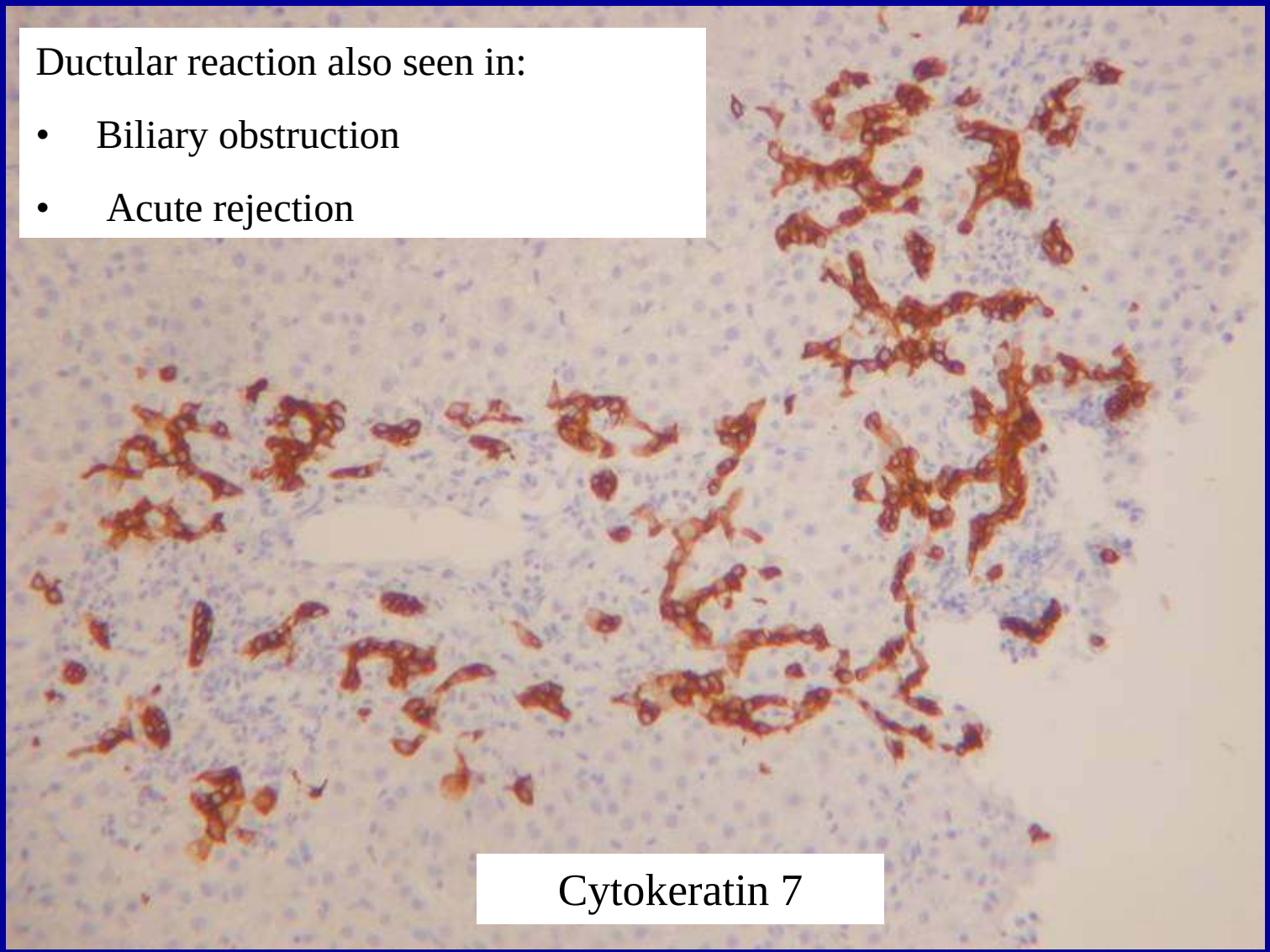
Female, age 50. Jaundice 3 months post-LT.



Cholestatic Hepatitis C
Female, age 50. Jaundice 3 months post-LT.

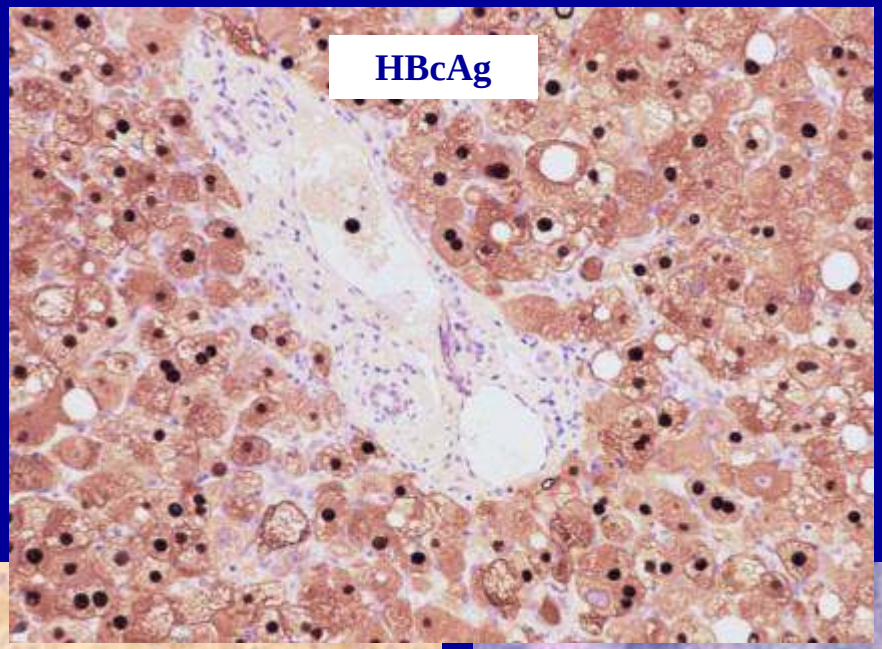
Ductular reaction also seen in:

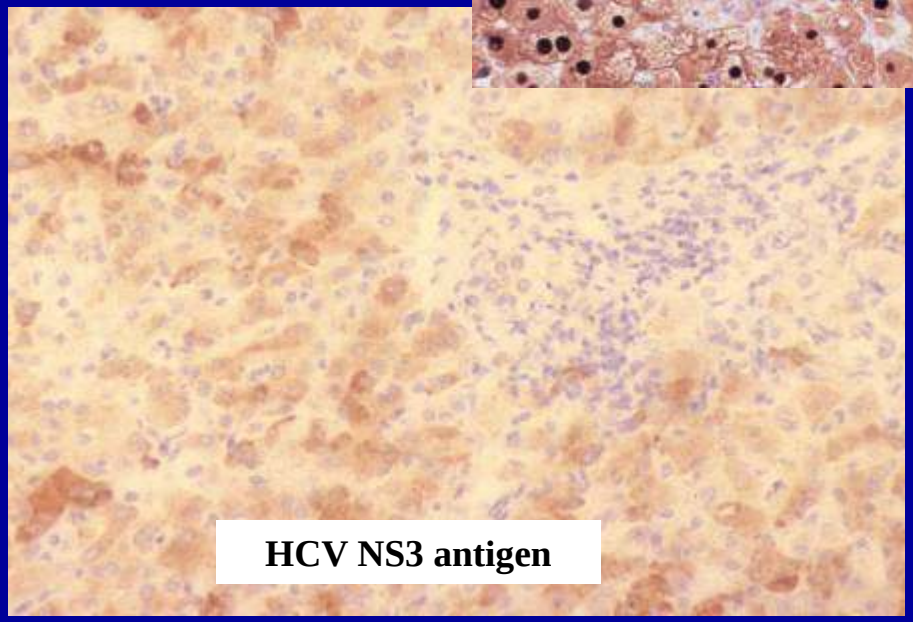
- Biliary obstruction
- Acute rejection

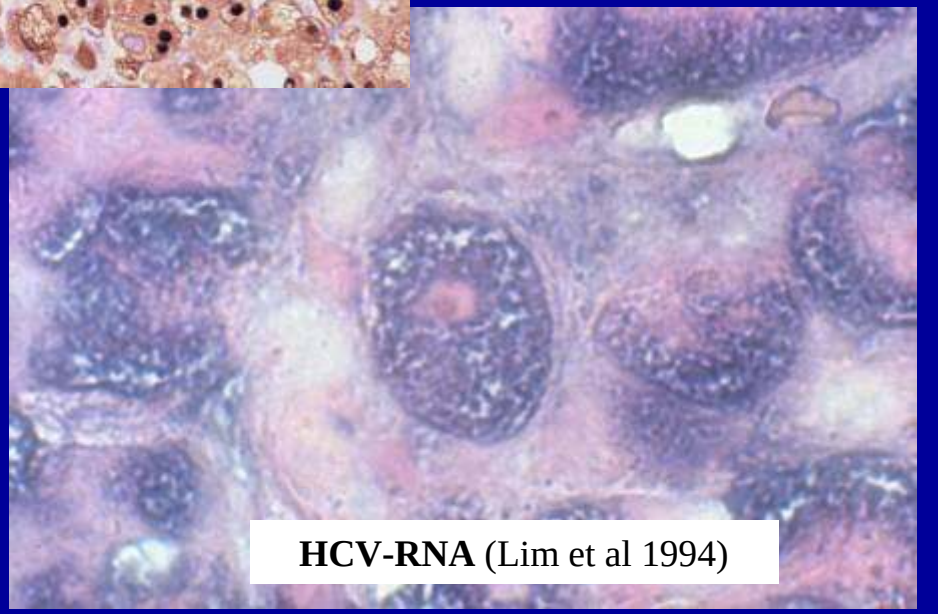


Cytokeratin 7

Cholestatic Viral Hepatitis in the Liver Allograft
High Level Expression of Viral Antigens/Nucleic Acids







Hepatitis C and Rejection

Rejection/immunosuppression = risk factors for severe/progressive HCV

- Immunosuppression allows increased viral replication
- Predisposes to more severe inflammation when immunosuppression reduced

Higher incidence of acute and chronic rejection in HCV-positive patients

- HCV-associated changes may augment alloimmune-mediated lesions
  - Common patterns of liver injury (e.g.portal inflammation, bile duct damage)
- Effects of anti-viral therapy (interferon)

Hepatitis C

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Rejection

Hepatitis C and Ac

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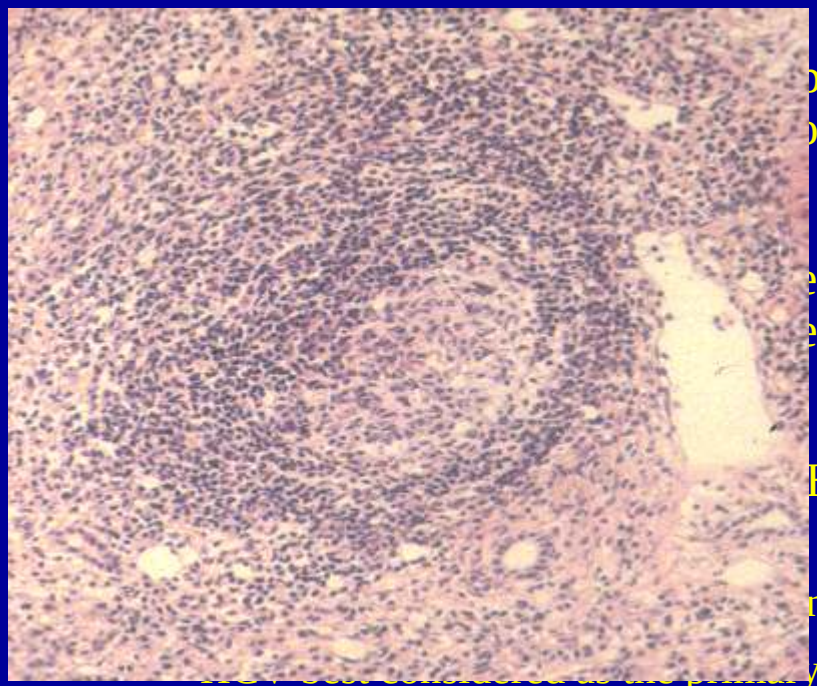

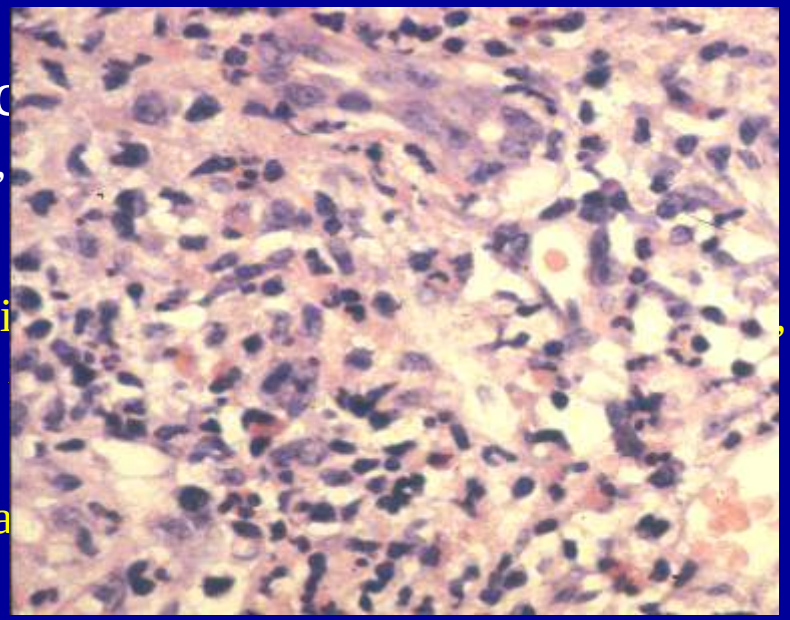

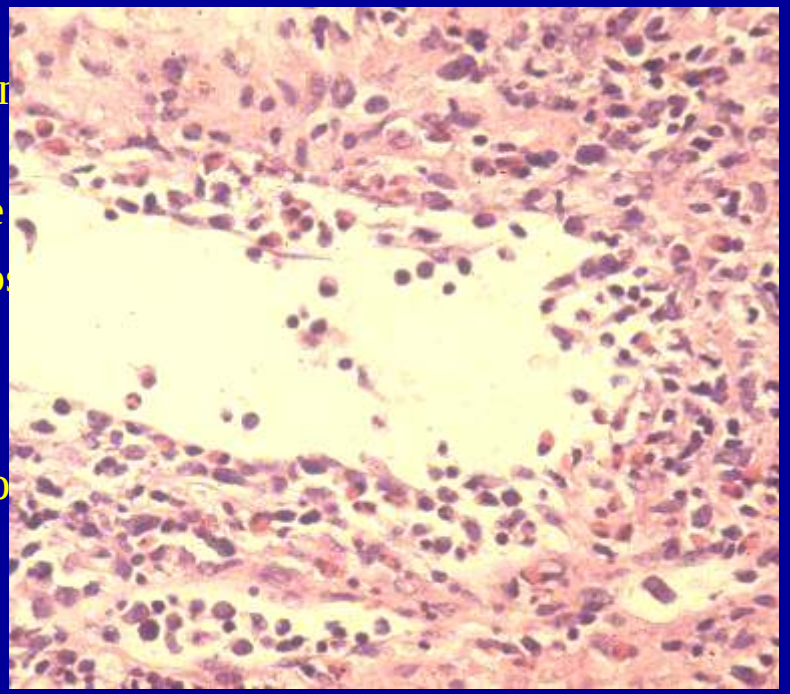

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- No additional immunosuppression required

- Increased immunosuppression should be co
  rejection changes moderate or severe

Hepatitis C with “Autoimmune Features” (de novo AIH)

Following Interferon Therapy (Cholongitas 2006,Kontorinis 2006,Berardi 2007,Merli 2009)

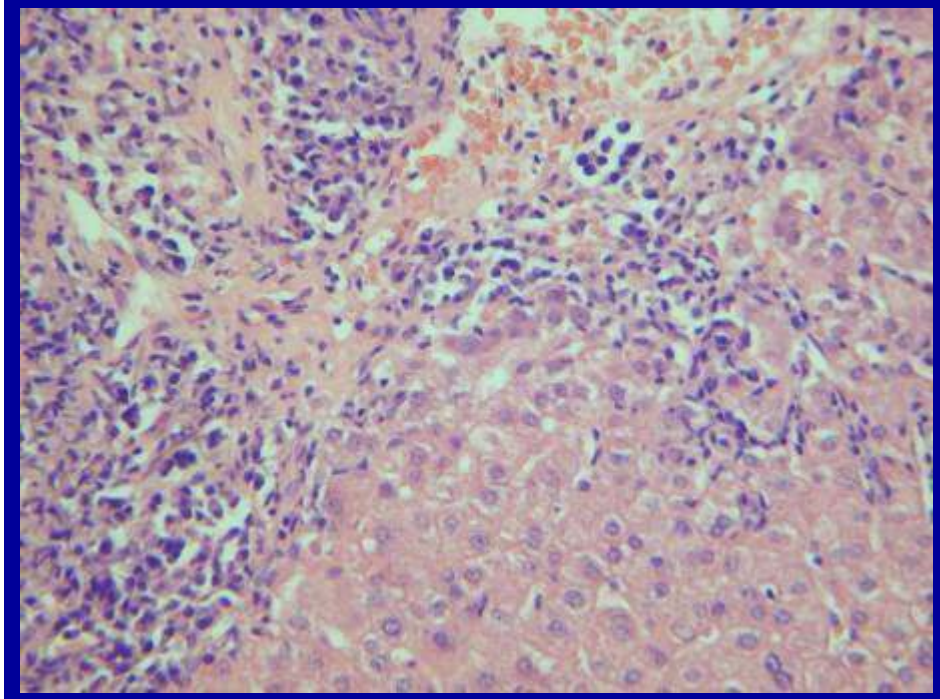
- 14 cases – all had biochemical, serological and histological features compatible with autoimmune hepatitis (“de novo AIH”)
- 12/14 were HCV-RNA negative
- 10/14 responded to treatment with immunosuppression

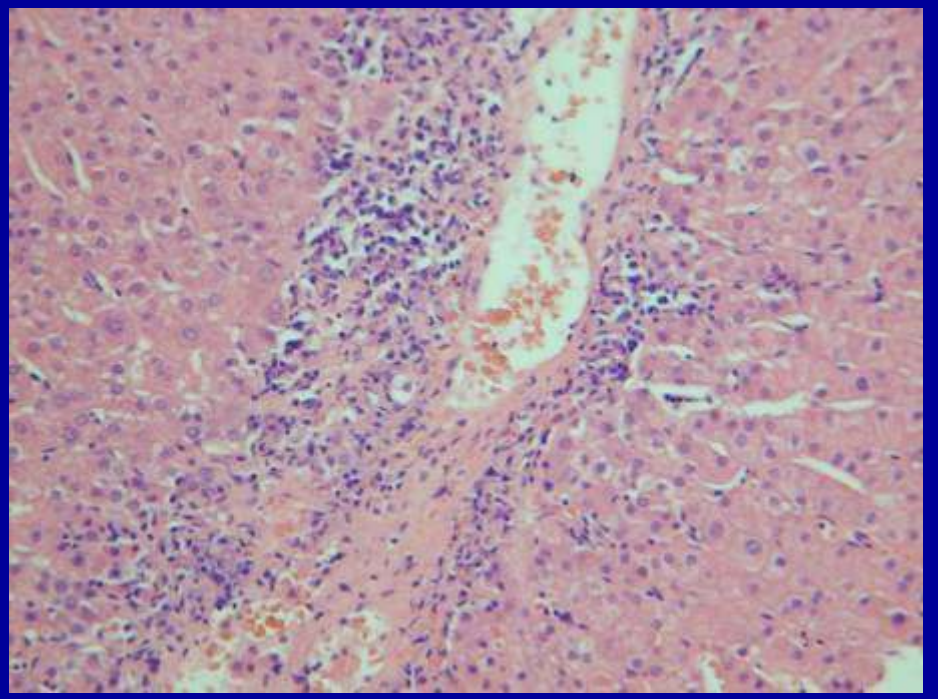
Unrelated to Interferon Therapy (Khettry 2007, Fiel 2008)

- 47 patients - plasma cell rich portal and lobular infiltrates (“plasma cell hepatitis”)
- Centrilobular necro-inflammatory changes (“central perivenulitis”) in 43/47
- Worse outcome than cases of “typical” recurrent HCV
  - Progression to cirrhosis, retransplantation or death

- 75% had increased serum immunoglobulins and/or autoantibodies (Khettry 2007)
- 82% had suboptimal immunosuppression, auto-antibodies only in low titre
  - Probably a form of rejection (Fiel 2008)

“De Novo” Autoimmune Hepatitis
Male,age 50. 2 years post-transplant– raised AST





Further investigations - IgG 24.90 g/L (normal 6.00-16.00), LKM antibodies positive1:100

Chronic Hepatitis E Virus Infection in Liver Allograft Recipients
Haagsma 2008, Kamar 2008, Gerolami 2008

- 11 transplant patients (5 liver, 4 kidney, 2 kidney/pancreas)
- All 11 patients developed biochemical and histological features of chronic hepatitis, with persistently elevated serum HEV-RNA levels
- Outcome variable:
  - 2 patients retransplanted with severe fibrosis/cirrhosis (Haagsma 2008)
  - Other 9 patients clinically well with persistently abnormal LFTs (raised AST/ALT). 7/9 have METAVIR fibrosis stage ≤ 2


The End……