Histological Assessment of Late Biopsies from the Liver Allograft

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Histological findings in 1108 biopsies obtained
> 1 year post-transplant, Liver Unit, QE Hospital, Birmingham

Main Diagnosis	**Number (%) Of Cases**	**Comments**
Normal / near normal	169 (15)	
Rejection	55 (5)	Many cases co-exist with other patterns of graft damage
Biliary obstruction / cholestasis	22 (2)	
Chronic hepatitis	402 (36)	94 (23%) cases related to recurrent disease 308 (77%) cases other/unknown cause
Recurrent disease	194 (18)	
Other findings	266 (24)	Fatty change, vascular/structural changes, fibrosis

Data from Liver Unit Database, Jan 2002 – Jan 2007

Reason for biopsy - 822 (74%) protocol, 286 (26%) clinically indicated

Many cases have more than one pattern of damage

Main Pathological Changes in Biopsies >12 Months Post-transplant

- Rejection
  - Less common than in early post-transplant period
  - May have different histological features
- Recurrent disease
  - General issues
  - Assessment of biopsies from HCV-positive individuals
- De novo disease
  - General issues
  - De novo autoimmune hepatitis
- Other findings in late biopsies
  - “Idiopathic” chronic hepatitis
  - Vascular/structural abnormalities

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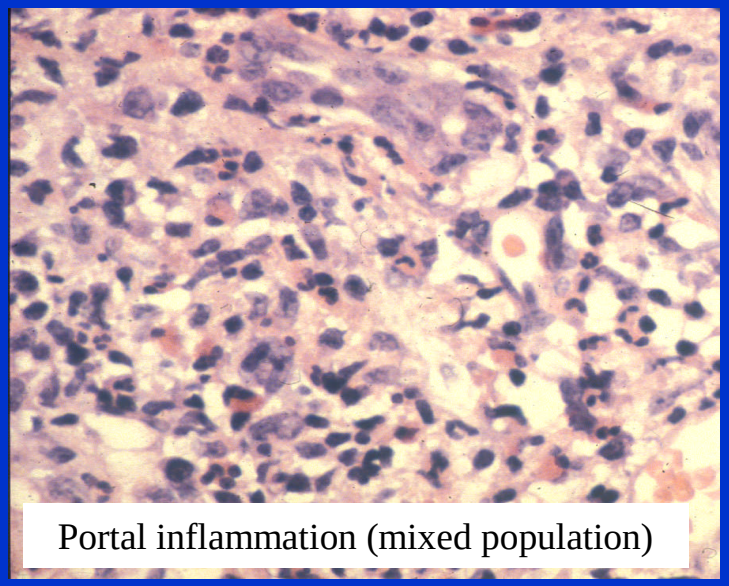
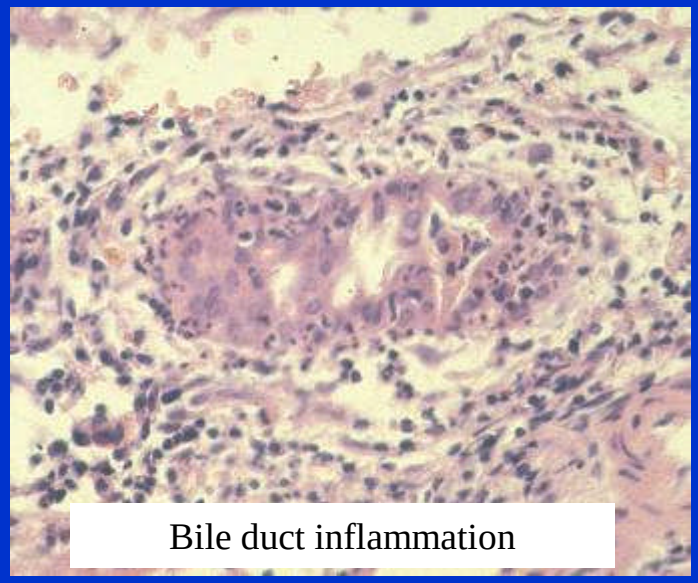
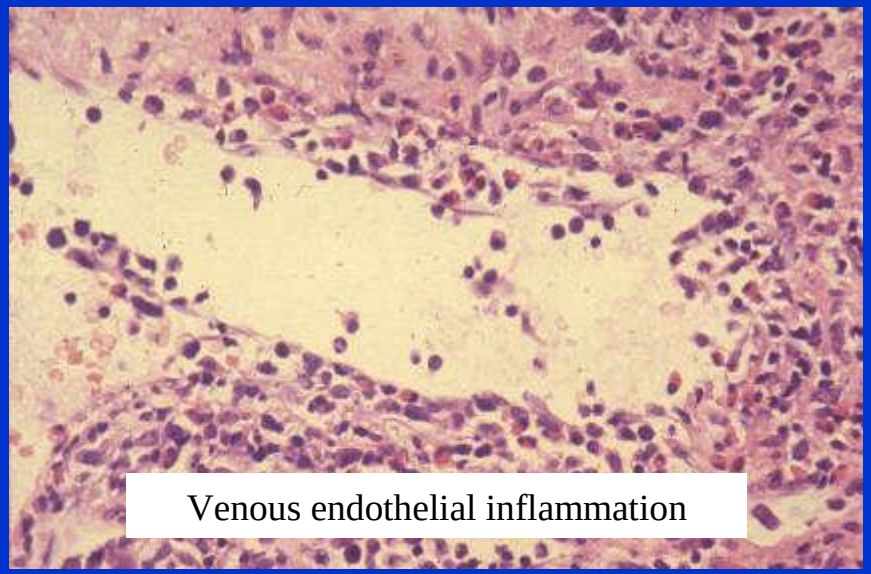
Acute Cellular Rejection – Typical Histological Features



Portal inflammation (mixed population)



Bile duct inflammation



Venous endothelial inflammation

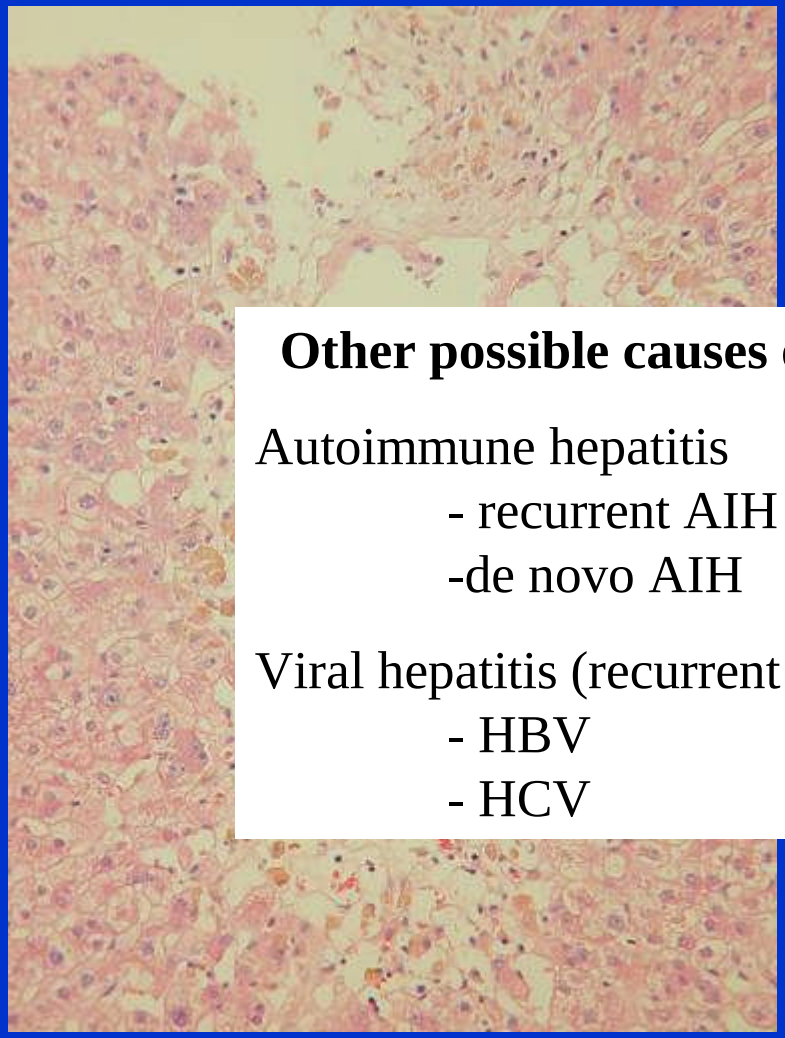
Late Cellular Rejection
Different Histological Features
(Snover 1988, Kemnitz 1989, Cakaloglu 1995, Pappo 1995)

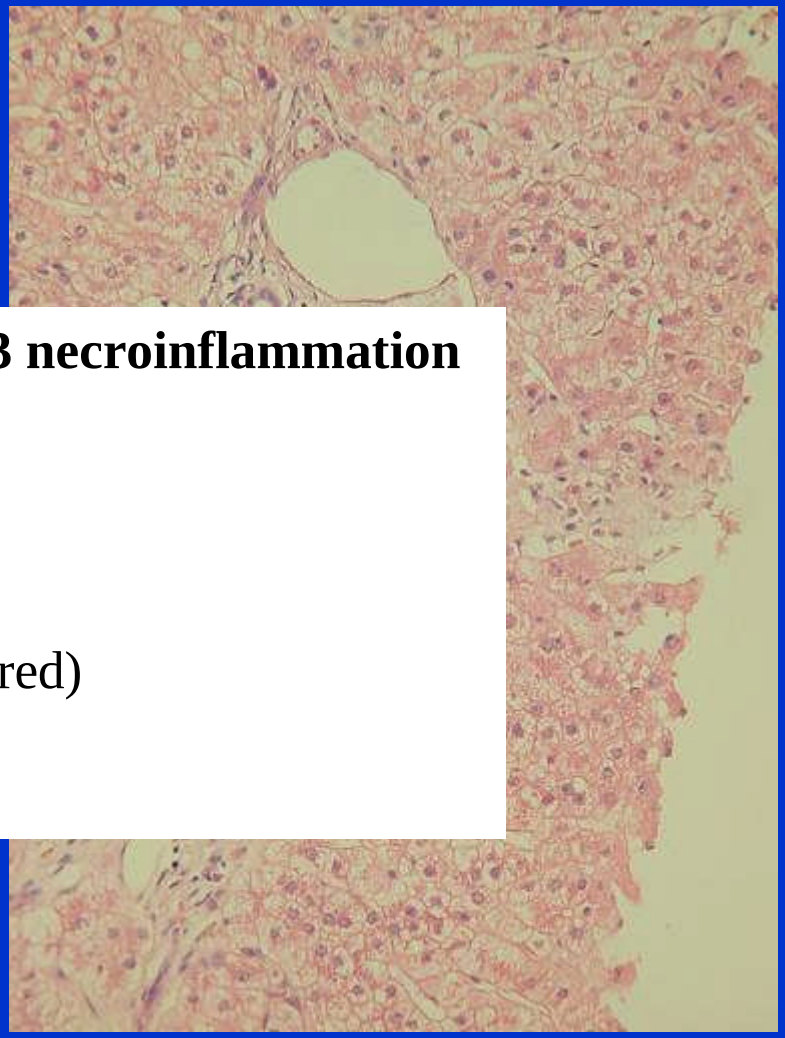
- Portal inflammation predominantly mononuclear
- Inflammation of bile ducts and venular endothelium less conspicuous
- More prominent interface hepatitis
- More prominent lobular hepatitis
- Overall features resemble those seen in chronic hepatitis
  (e.g. viral or autoimmune)

- More recent studies suggest that zone 3 necroinflammatory lesions ("central perivenulitis") may also be a feature of late cellular rejection
  (Banff Working Party, Hepatology 2006; 44: 489-501)
- Central perivenulitis may occur as an isolated lesion (without typical portal rejection changes)

Liver Allograft Rejection - “Central Perivenulitis”

Liver biopsy, 6 months post-transplant. Worsening LFTs (AST 2xN)





Other possible causes of zone 3 necroinflammation

Autoimmune hepatitis

- recurrent AIH
- -de novo AIH

Viral hepatitis (recurrent or acquired)

- HBV
- HCV

Central Perivenulitis in Liver Allograft Rejection

(Gouw 2002, Neil 2002,Sebagh 2002, Lovell 2004, Hassoun 2004, Junge 2005, Riva 2006, Sundaram 2006)

Clinico-pathological Features

- Present later than cases with pure portal rejection
- Often associated with raised transaminase levels
- Less responsive to immunosuppression
- More likely to progress to chronic rejection

Clinical Significance

- Transitional phase between acute (reversible) rejection and chronic (irreversible) rejection
- Precedes bile duct loss
- Early recognition and prompt treatment can prevent progression to chronic rejection (graft failure due to chronic rejection now < 2%)

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Disease Recurrence in the Liver Allograft

DISEASE	FREQUENCY
HEPATITIS B	< 10% (up to 85% in earlier studies)
HEPATITIS C	> 80%
PBC	30-40%
PSC	20-30%
AUTOIMMUNE HEPATITIS	20-30%
ALCOHOL	10 - 30%
NASH (“cryptogenic” cirrhosis)	20-40%

Recurrent disease = commonest cause of late graft dysfunction

Disease Recurrence in Liver Allografts -Diagnostic Problems
(1) Recurrent disease and other transplant complications

(A) Histological Similarities

- Hepatitis C v Acute rejection
- PBC/PSC v Chronic rejection
- PSC v Ischaemic biliary complications

(B) Other Interactions

- Higher incidence of rejection (acute and chronic) in:
  - patients transplanted for autoimmune liver disease
  - recurrent HCV

- Changes seen in late biopsies often reflect more than one pathological process
- Clinical picture often complex
- Histology may help to identify the dominant cause of graft damage

Disease Recurrence in Liver Allografts -Diagnostic Problems
(2) Effects of immunosuppression

LESS aggressive disease	-	immune - mediated disease (e.g. AIH, PBC)
MORE aggressive disease (atypical patterns)	-	viral hepatitis (e.g. HBV,HCV)

Hepatitis C in the Liver Allograft

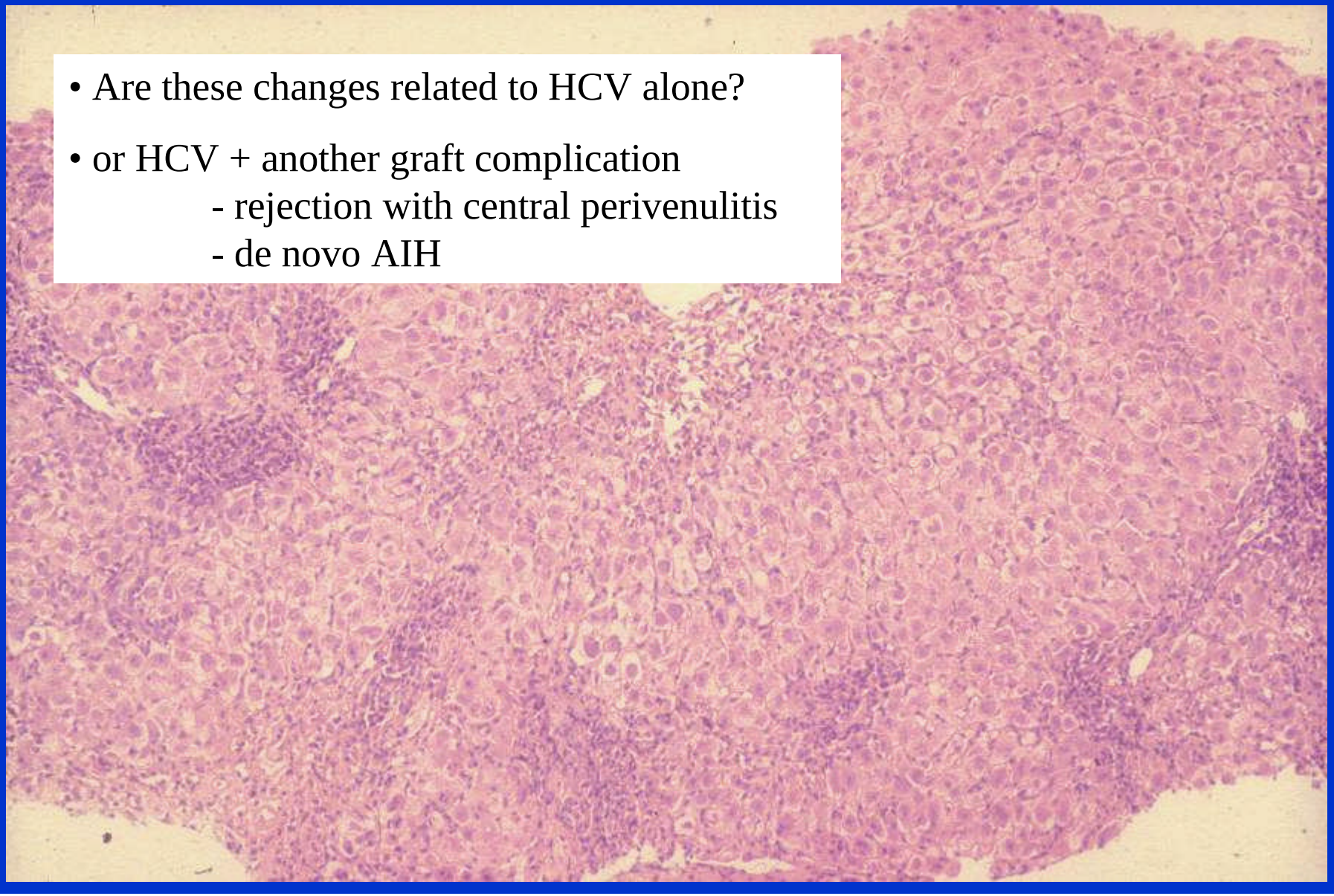
- HCV cirrhosis commonest indication for liver transplantation
- Re-infection is universal (occurs within a few hours)
- Most cases (>80%) develop graft inflammation
- Many progress to cirrhosis
  - 20% by 5 years, up to 50% at 10 years
- Reduced graft and patient survival

Hepatitis C in the Liver Allograft
Differences Compared with HCV in the Native Liver

- More aggressive disease
  - More severe inflammatory activity (more rapid progression to fibrosis and cirrhosis)
  - Cholestatic features (fibrosing cholestatic hepatitis)

- Hepatitis C and rejection

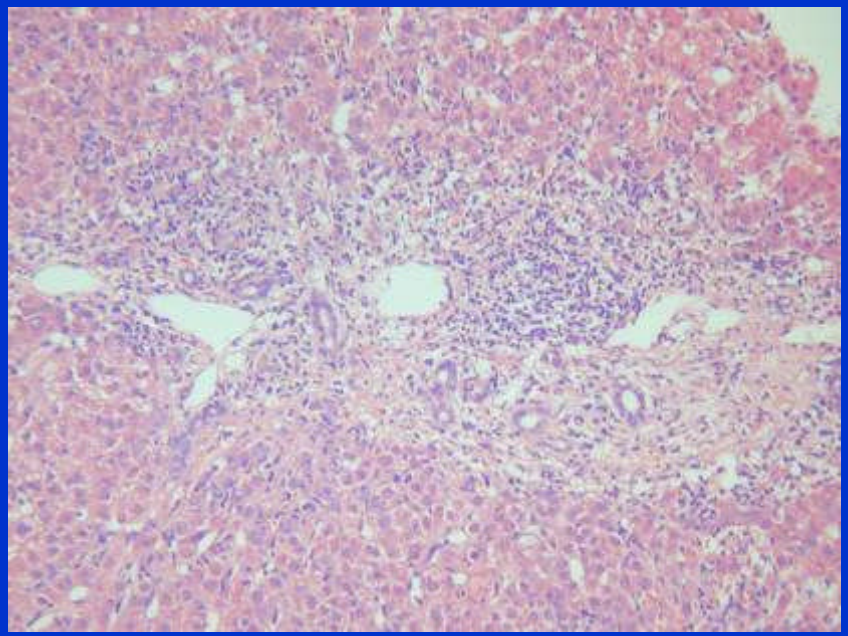
Recurrent Hepatitis C
prominent lobular inflammation with zone 3 necrosis

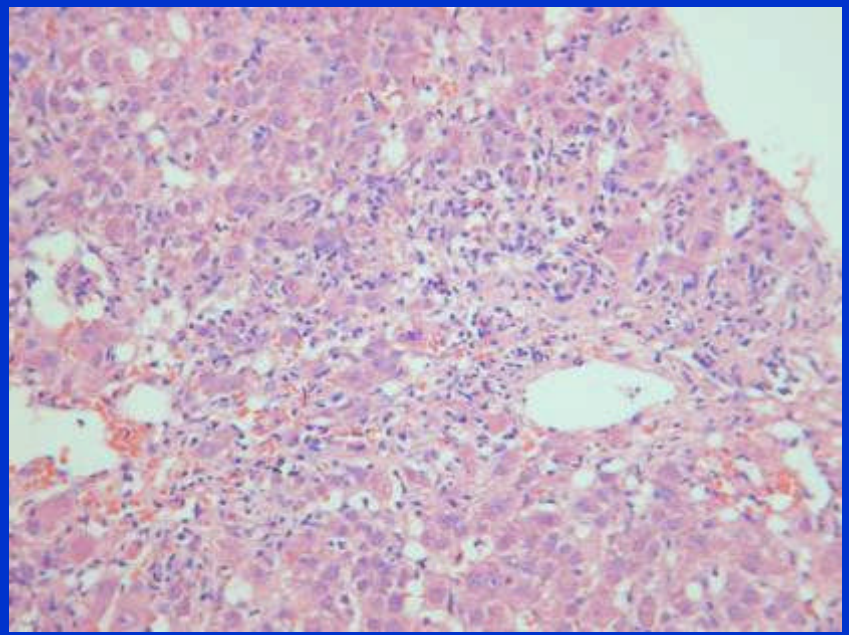


- Are these changes related to HCV alone?
- or HCV + another graft complication
  - rejection with central perivenulitis
  - de novo AIH

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



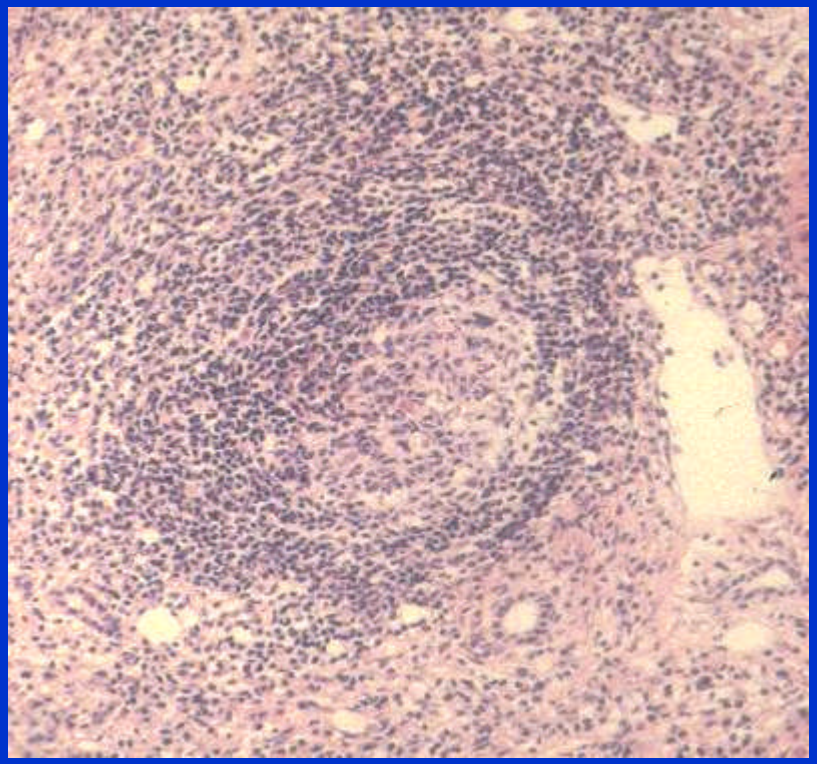


HEPATITIS C

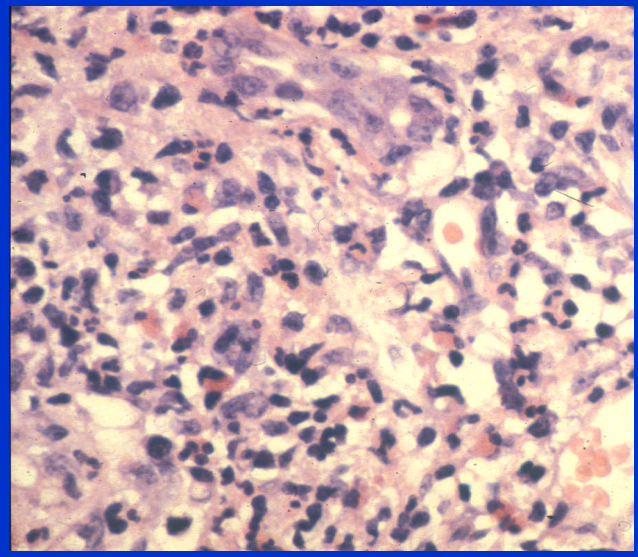
VERSUS

CELLULAR REJECTION

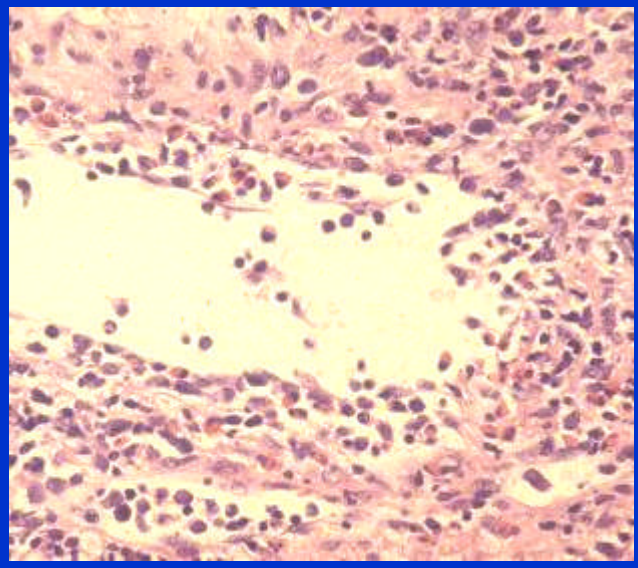
Hepatitis C versus Cellular Rejection -Portal Inflammatory Lesions



Hepatitis C



Rejection



HEPATITIS C

~~VERSUS~~

AND

CELLULAR REJECTION

Recurrent Hepatitis C and Acute Rejection

(Demetris et al. Am J Surg Pathol 2004; 28: 658-699)

- Recognition that AR and recurrent HCV overlap in time and histological features
- Prospective study of biopsies from 48 HCV positive patients
  - Identify main cause of graft damage
  - Verify diagnosis by subsequent clinical course
- In most cases where dual pathology suspected rejection changes are mild
  - HCV best considered as the primary diagnosis
  - No additional immunosuppression required
- Increased immunosuppression should be considered as a treatment option if rejection changes moderate or severe

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De Novo Disease in the Liver Allograft

DISEASE	*DE NOVO* OCCURRENCE
Hepatitis B	YES
Hepatitis C	YES
PBC	NO
PSC	NO (but ischaemic cholangitis resembles PSC)
Autoimmune Hepatitis	YES
Alcohol	Possible
NASH	YES

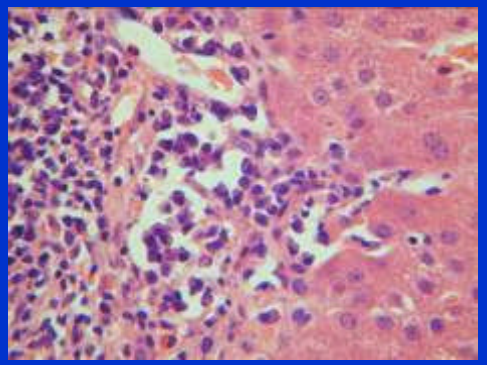
‘De Novo’ Autoimmune Hepatitis in the Liver Allograft

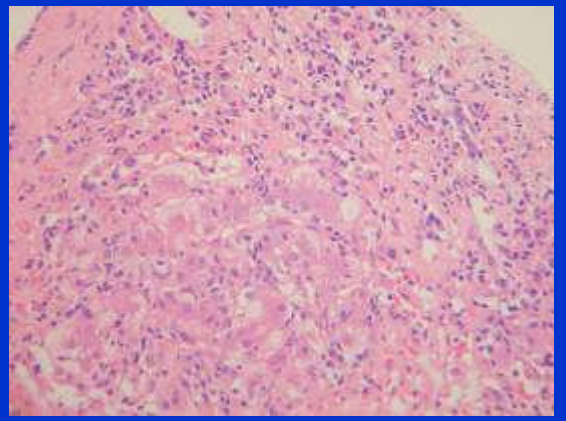
(Kerkar 1998, Jones 1999, Gupta 2001, Heneghan 2001, Salcedo 2002, D’Antiga 2002, Miyagawa-Hayashino 2004, Mieli-Vergani 2004, Aguilera 2004 & 2005, Riva 2006, Rodriguez-Mahou 2007).

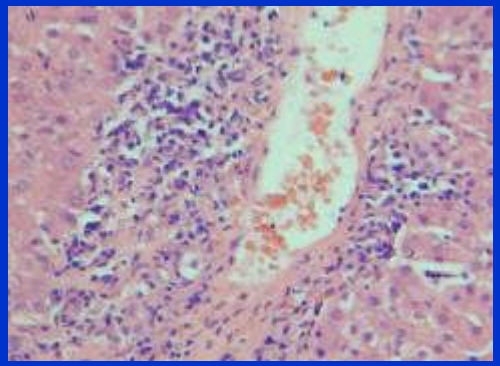
1. Classical biochemical, serological and histological features of AIH may develop in patients transplanted for other diseases
2. Higher prevalence in paediatric population (5-10%), compared with adults (1-2%)
   ? Immunosuppressive drugs interfering with normal T cell maturation
3. Most cases respond to increased immunosuppression. Occasional cases have progressed to graft failure
4. Areas of overlap between de novo AIH and rejection
   - antibodies to graft antigens may indicate an alloimmune response
   - de novo AIH could represent a form of late cellular rejection

Chronic Hepatitis in the Liver Allograft
Features favouring an autoimmune aetiology

- Portal inflammation with numerous plasma cells
- Prominent interface hepatitis
- Lobular inflammation (plasma cell rich) with zone 3 necrosis
- Lobular changes in de novo AIH more prominent than in AIH in the native liver (Salcedo 2002, Aguilera 2004)







Pegylated Interferon Therapy for HCV and De Novo AIH

	Number of cases
Cholongitas Transplantation 2006;81:488-90.	1
Kontorinis Liver Transpl. 2006;12:827-30.	1
Berardi Gut 2007;56:237-42.	9/44 patients

- All 11 cases had biochemical, serological and histological features compatible with AIH
- 9/11 were HCV-RNA negative
- 7/11 responded to treatment with immunsuppression

Patterns of recurrent hepatitis C after liver transplantation
(Khettry Human Pathol 2007; 38: 443-452)

- 61 cases of recurrent HCV
  - 52 “typical” recurrent HCV
  - 9 “AIH-like”

- Histological Findings in “AIH-like” HCV
  - Plasma cell-rich infiltrate (portal and/or lobular)
  - Higher frequency of central perivenulitis (5/9 vs 8/52 typical HCV)
  - More rapid fibrosis progression

- Other Findings in “AIH-like” HCV
  - Increased serum immunoglobulins and/or autoantibodies (6/8 cases)

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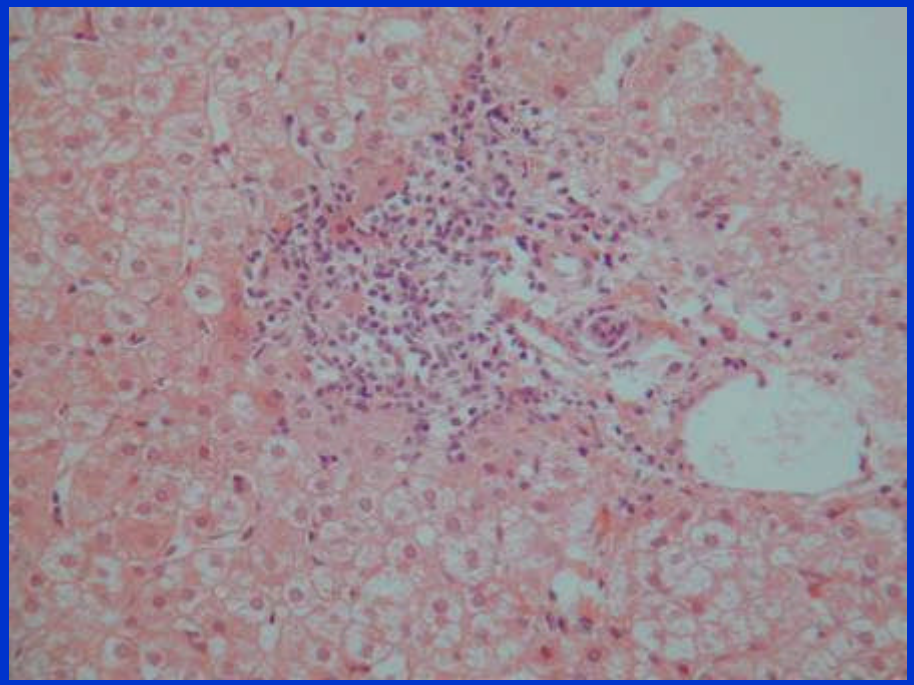
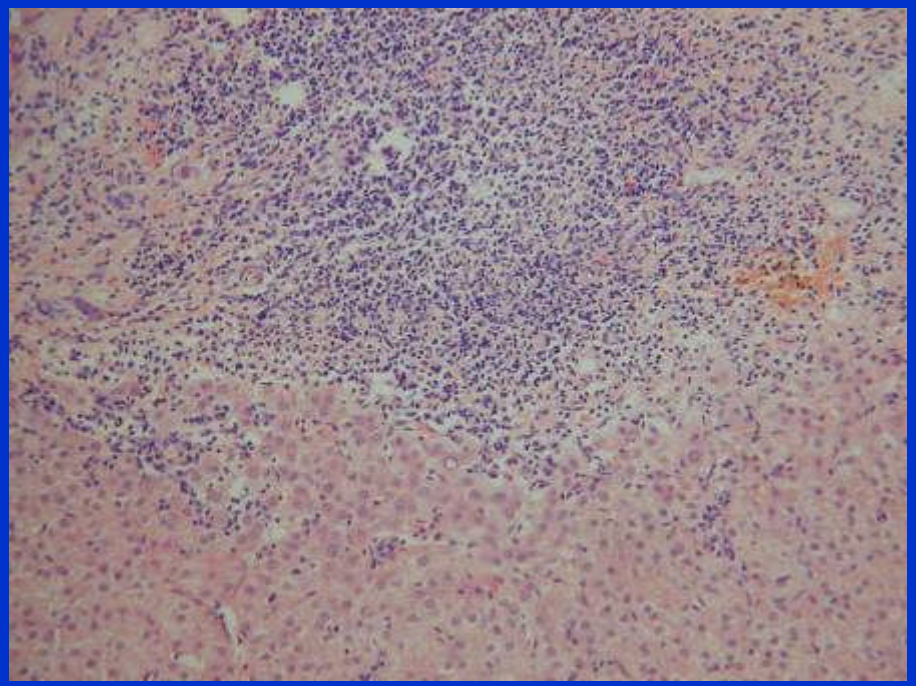
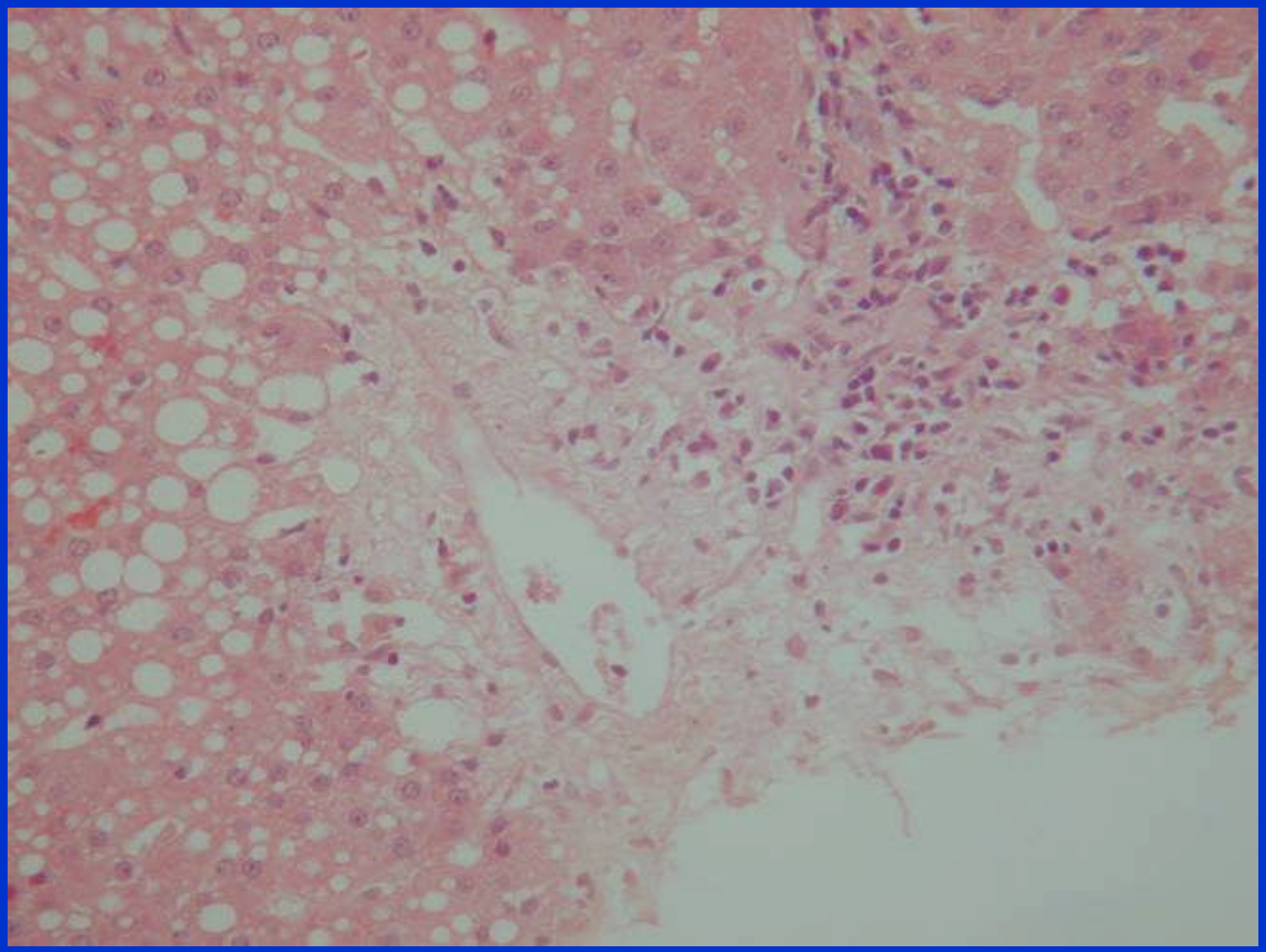
  - De novo autoimmune hepatitis
- Other findings in late biopsies
  - "Idiopathic" chronic hepatitis
    - Commonest histological diagnosis in late post-transplant biopsies
    - In cases where viral and autoimmune causes have been excluded, could this be a form of rejection?

Chronic Hepatitis in the Liver Allograft
Portal Inflammatory Changes





Chronic Hepatitis in the Liver Allograft
Lobular Inflammatory Changes



Chronic Hepatitis in Late Post-Transplant Biopsies
Could this be a form of late cellular rejection?

- In the adult population, excluding recurrent disease as a cause for chronic hepatitis is difficult
  - Most of the diseases for which transplantation carried out in adults have the potential to recur, with features of chronic hepatitis
  - Histological features of "non-specific" chronic hepatitis may precede other diagnostic abnormalities of recurrent disease (AIH and PBC)

- Alternative Approaches
  - Paediatric patients
  - Adults transplanted for non-recurring diseases

Progressive histological damage following paediatric liver transplantation

Evans HM, Kelly DA, McKiernan PJ, Hübscher SG Hepatology 2006; 43: 1109-1117

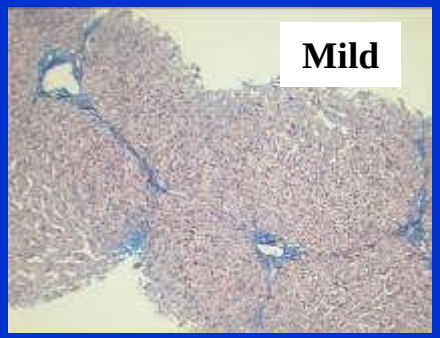
- 158 patients followed for > 5 years post-transplant
- Only 8 transplanted for diseases known to recur
  - 5 primary sclerosing cholangitis
  - 3 autoimmune hepatitis
- Protocol biopsies at 1, 5 and 10 years

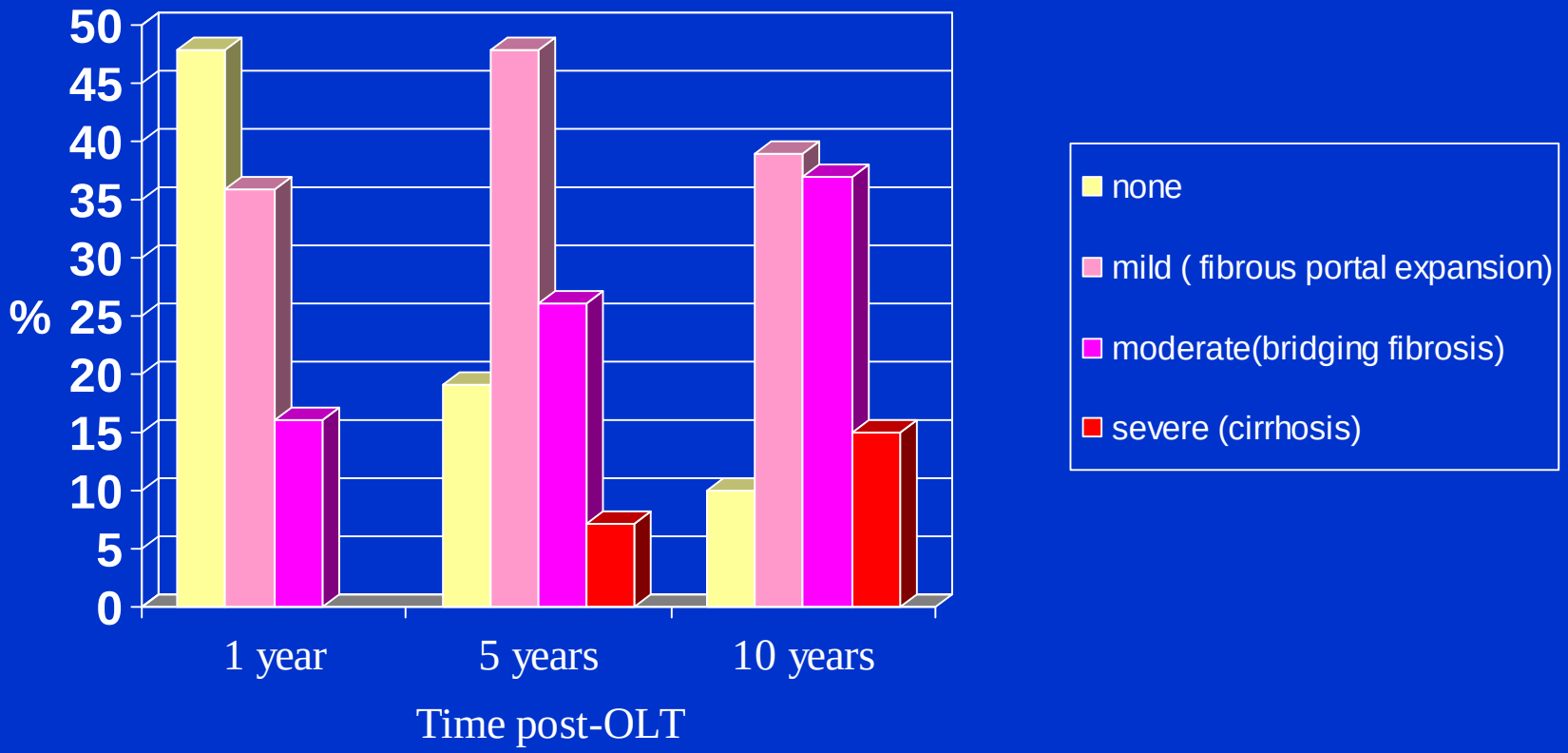
Progressive histological damage following paediatric liver transplantation

Evans HM, Kelly DA, McKiernan PJ, Hübscher SG Hepatology 2006; 43: 1109-1117

Histological Diagnosis	1 year (n=113)	5 years (n=135)	10 years (n=64)
Normal/ near normal	68.2%	45.2%	31.3%
Chronic hepatitis	22.1%	43.0%	64.0%
Rejection (acute or chronic)	2.7%	2.2%	0
Biliary obstruction	6.2%	7.4%	1.6%
Recurrent Disease	0.9%	0.7%	1.6%
Other	0	1.3%	1.6%

Chronic Hepatitis - Severity of Fibrosis at Different Times





Further findings in chronic hepatitis cases

- 70-80% associated with auto-antibodies, many in high titre

  (vs 10-13% in cases with normal histology, all in low titre – ANA $\leq$ 1 in 40)

- Only 6% fulfil other diagnostic criteria for *de novo* autoimmune hepatitis
  - Median AST levels < 2xN

Natural history of unexplained chronic hepatitis following liver transplantation

(Syn WK, Nightingale P, Gunson B, Hubscher SG, Neuberger JM. Liver Transplantation 2007, 13: 984-9)

- 288 / 1968 adults transplanted in Birmingham (1982-2005) without features of disease recurrence
  - Alcoholic liver disease, with no significant alcohol consumption post-LT (n= 201)
  - Drug-induced acute liver failure (n= 87)

- 46/143 (32%) patients biopsied > 6 months had chronic hepatitis
  - Median time of diagnosis 15 months (6-72)

Natural history of unexplained chronic hepatitis following liver transplantation

(Syn WK, Nightingale P, Gunson B, Hubscher SG, Neuberger JM. Liver Transplantation 2007, 13: 984-9)

Follow -up

- 30/ 46 patients with chronic hepatitis had one or more subsequent biopsies
  - median time from index to latest biopsy 3.9 years (range 0.6- 9.4)
  - Fibrosis progressed in 13, same in 14, improved in 3

- Factors correlating with fibrosis progression
  - High titre autoantibodies (ANA > 1:1600)
  - Plasma cell rich infiltrate in index biopsy
  - Female donor sex
  - Alkaline phosphatase levels

Chronic Hepatitis with “Autoimmune Features”
Clinical Implications

Graft Monitoring

- routine LFTs unreliable
- protocol biopsies
- autoantibody testing

Treatment (immunosuppression to prevent disease progression?)

- criteria for treatment
- monitoring therapeutic responses
- patients transplanted for hepatitis C

Many patients have mild changes with no evidence of fibrosis

- Does mild (non-progressive) portal hepatitis represent a form of graft tolerance?
- Can liver biopsy help to identify patients in whom immunosuppression can be reduced or withdrawn?

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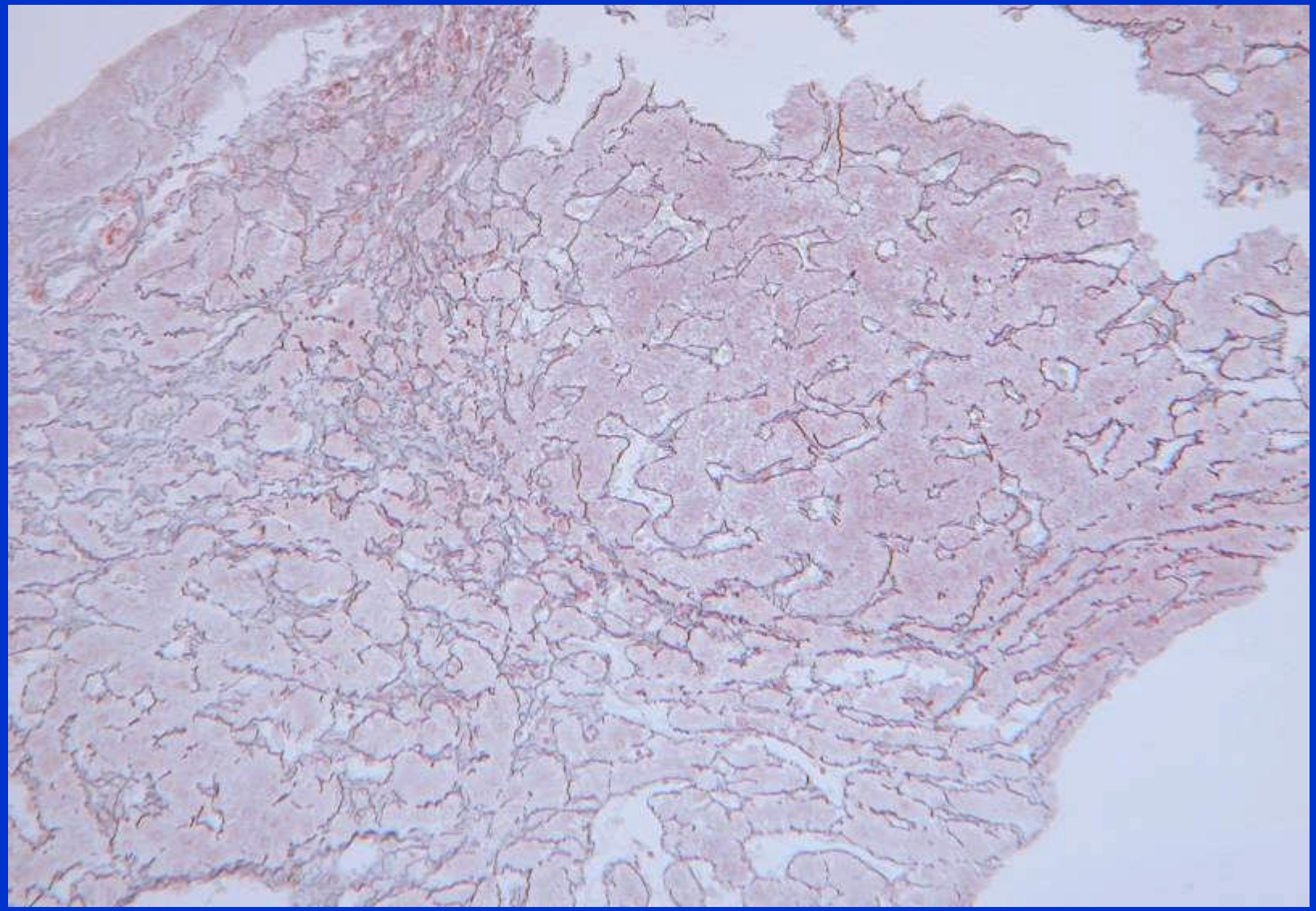
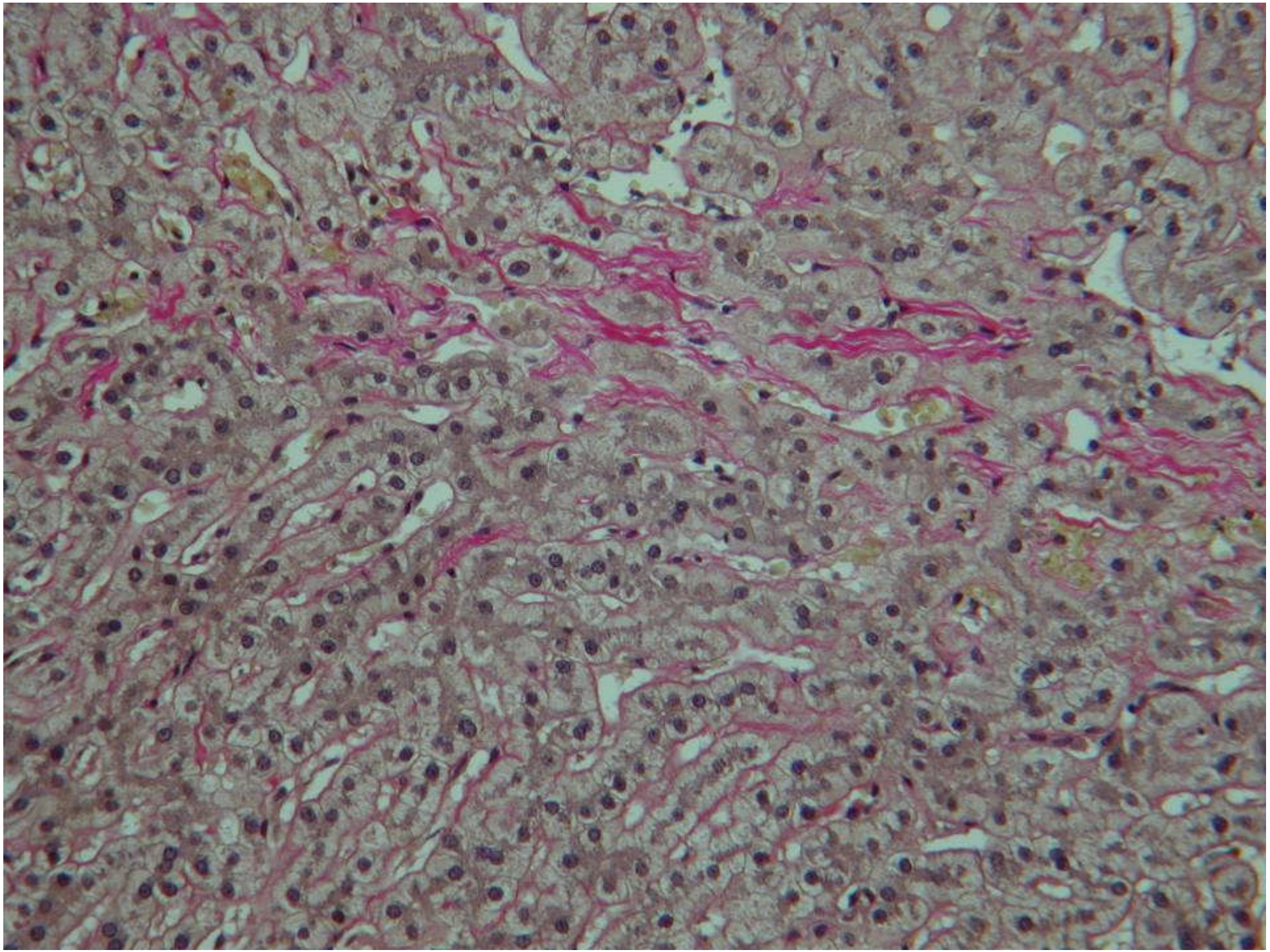
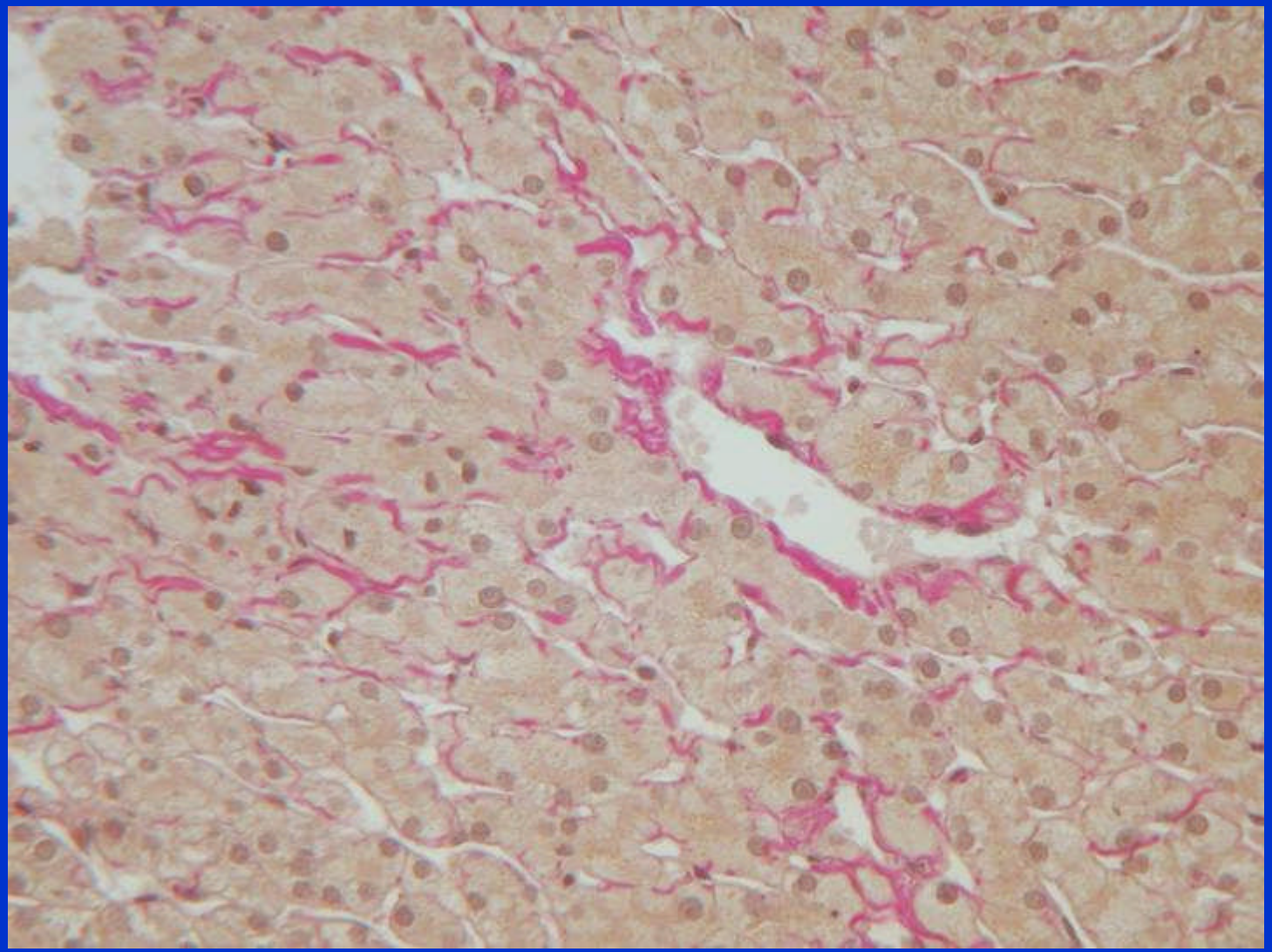
Nodular Regenerative Hyperplasia

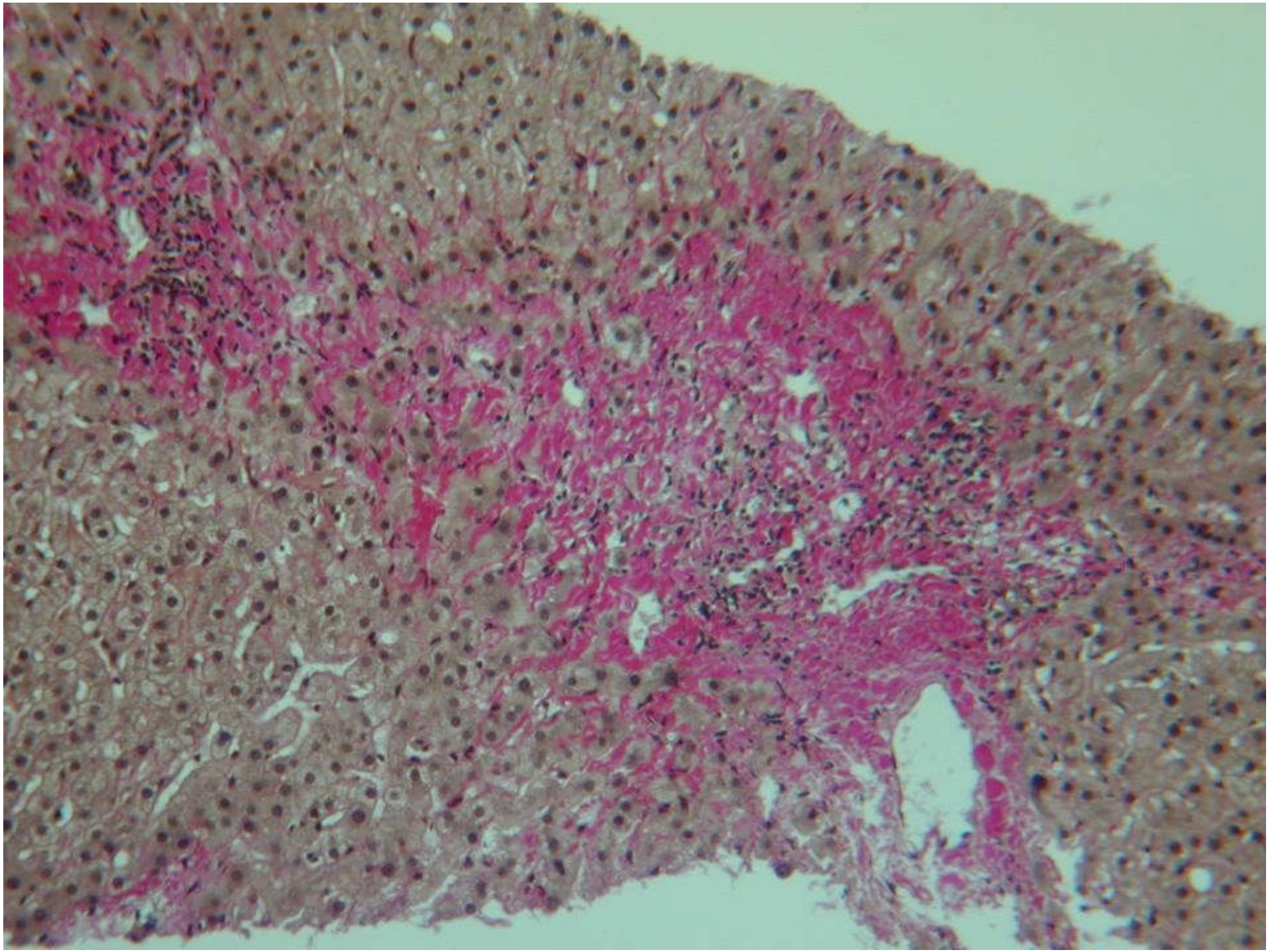
Male age 46 – protocol biopsy 12 months post-transplant for Wilson's disease





Perisinusoidal Fibrosis





Nodular changes in late post-transplant biopsies

(Pappo 1995, Slapak 1997, Sebagh 2003, Devarbhavi 2007)

- Frequency 2% - 82%

- Possible Causes (impaired sinusoidal blood flow)
  - Vascular problems (portal/hepatic venous insufficiency)
  - Drug toxicity (azathioprine)
  - Immune mediated (rejection related damage to sinusoidal/vascular sinusoidal endothelium)

- Clinical Consequences
  - 6/26 cases reported from KCH London required retransplantation (Slapak Hepatology 1997; 25: 195-202)
  - 7/14 cases from Mayo Clinic symptomatic with features of portal hypertension (ascites -7, varices- 4) (Devarbhavi Liver Transpl. 2007;13:1552-6.)
  - Others noted as incidental finding

Liver Biopsy Interpretation for Causes of Late Liver Allograft Dysfunction

Banff Working Group[1]

(HEPATOLOGY 2006;44:489-501.)

Idiopathic Posttransplantation Hepatitis?

Obaid S. Shaikh[1] and A. Jake Demetris[2]

LIVER TRANSPLANTATION 13:943-946, 2007

The Significance of Nodular Regenerative Hyperplasia in the Transplanted Liver

Alyssa Krasinskas

LIVER TRANSPLANTATION 13:1496-1497, 2007