UK Liver Transplant Meeting 2017

Cambridge case

57 male

- Liver transplant Nov 2014
  ASH/NASH/haemochromatosis
- Duct-to-duct anastamosis
- DBD moderately steatotic
- Episode of acute cellular rejection at 1 month treated with 3 days of methylprednisolone
- Korsakoff's syndrome (in care home)
- Morbidly obese (145 kg)
- T2 DM
- Hypertension

Mild reperfusion injury at baseline.

Cont…

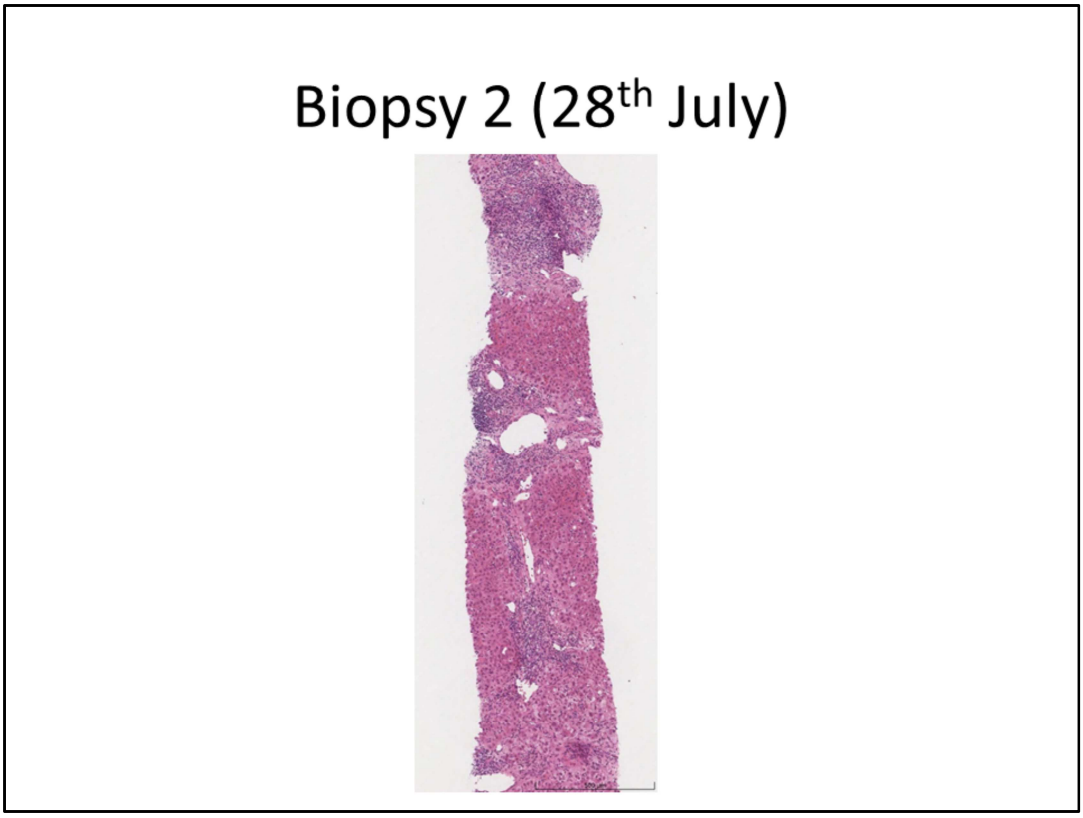
- FU elsewhere
- Abnormal LFT in May 2016 (biopsy 1)
- Treated for genital herpes in Jan 2017
- Presented with this episode on 23rd July
- Abdominal cramps, diarrhoea for 4/7 then jaundice
- No new treatment
- Continued to take regular medications (Tac 0.5mg bd)
- Viral screen negative
- Bil 312, ALP 378, ALT 153 (biopsy 28th July)
- LFTs normal prior to this episode

Regular meds ? compliance

Biopsy 2 (2 years, 9 months post transplant)

Biopsy 2 (Slide 382053) 2 years, 9 months. Biopsy taken following 6 days of abdominal cramps and diarrhoea. Viral serology screen negative.

Biopsy 3 (Slides 382054, 382055, 382056 and 382057) 9 days after Biopsy 2. Worsening LFTs despite treatment with pulsed methylprednisolone. Bil 506, ALP 917, ALT 800. Patent vasculature on US liver doppler and triple phase CT. MRCP suggest cholangiopathy.



These slides were kindly sent for review following patient transfer from Southampton to Addenbrooke's Hospital.

They show long, thin cores which are partially composed of extrahepatic adipose tissue and fibrovascular connective tissue, along with a short, thin sample of liver tissue, in which portal tracts are poorly represented, hampering interpretation. Architecture is difficult to assess, but there appears to be portal fibrous expansion, along with variable periportal sinusoidal fibrosis, with possible portal-portal broad fibrous septa, but without definite nodule formation.

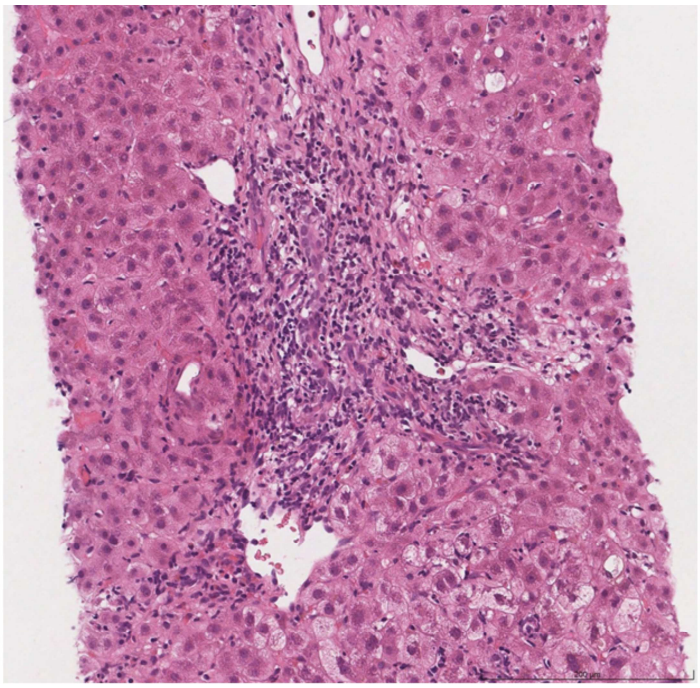
Portal areas are not well visualised, but where assessable contain a chronic inflammatory cell infiltrate which includes occasional blasts and eosinophils, as well as plasma cells, ceroid-laden macrophages and a patchy neutrophilic infiltrate, with focal spillover of inflammatory cells at the limiting plate. Bile ducts show a variable degree of inflammatory and degenerative atypia with focal cholangiolitis and minor ductular reaction with possible focal ductopaenia, although bile ducts appear present where assessable. Portal veins appear ectatic in places and there is focal and segmental portal vein endothelialitis.

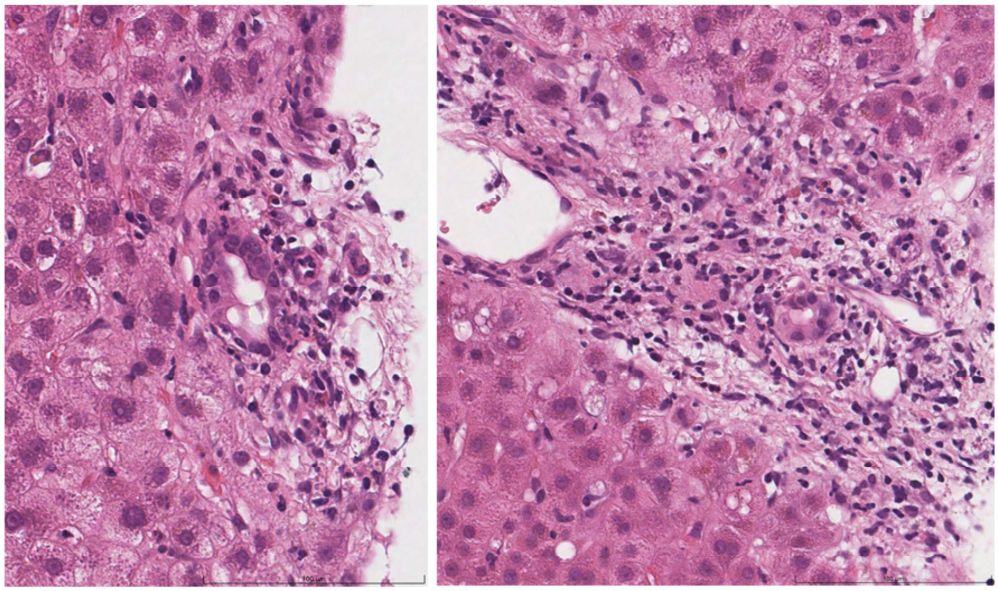
The parenchyma shows lobular disarray with regenerative appearing cell plates, cellular and canalicular cholestasis, Kupffer cell hyperplasia, lymphocytosis and patchy necroinflammation, including acidophil bodies and focal haemorrhage

into cell plates. Scattered multinucleated hepatocytes are present. There is minor focal steatosis without features of steatohepatitis. Terminal hepatic vein endothelialitis is focal and slight.

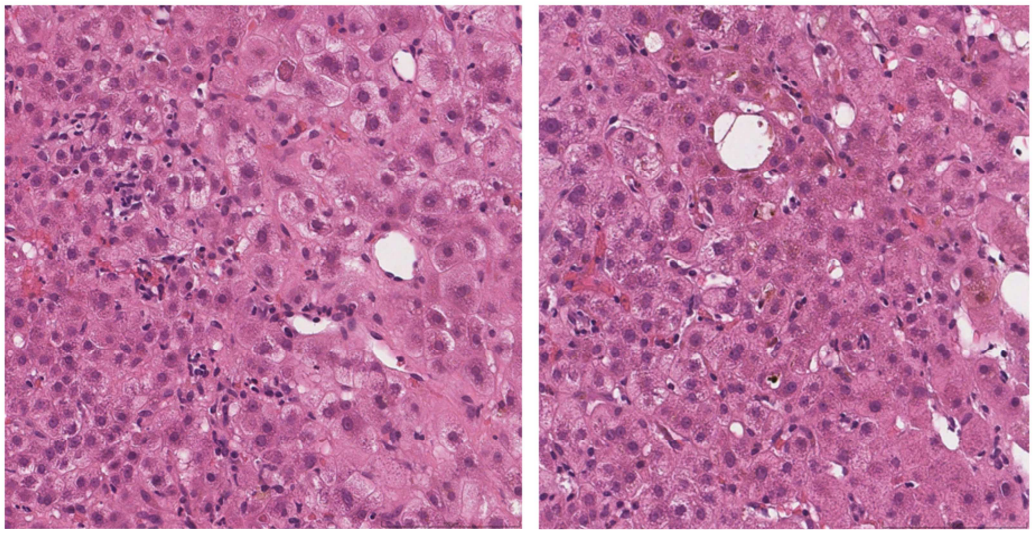
There is a patchy grade 1 siderosis of hepatocytes, with iron also present within Kupffer cells. No alpha-1 antitrypsin material or copper associated protein is evident.

Final Diagnosis
Liver graft biopsy, 2 years 9 months - there is a portal and lobular hepatitis with cholestasis and background periportal fibrosis. A rejection inflammatory infiltrate is present and although 'atypical' late cellular rejection is a consideration, the degree of cholestasis and lobular activity seems excessive for rejection alone and viral and drug causes should therefore be excluded in the first instance.





Focal cholangitis



Treated as rejection

- Tacrolimus increased from 0.5mg to 1mg
- Three days IV methylprednisolone

Given the rejection inflammatory infiltrate – treated as rejection

Bloods

	Bili	ALT	ALP	INR	
23/7	247	234	374		
25/7	263	206	338		
26/7	271	188	357		
27/7	316	167	371		
28/7	312	153	378		MP 500mg
29/7	388	145	437	1.2	MP 500mg
30/7	370	143	411	1.2	MP 500mg
31/7	334	203	415	1.2	20mg pred
01/8	379	281	452	1.2	20mg pred
02/8	416	497	-	1.2	30mg pred
03/8	376	541	560	1.1	
04/8	436	606	-	1.3	

Transferred to Addenbrooke's 4th Aug

- US Doppler Liver And Portal System
  - Patent vasculature. No cause for deterioration in liver function demonstrated
- Triple phase CT and MRCP
- Liver biopsy (liver biopsy 3)

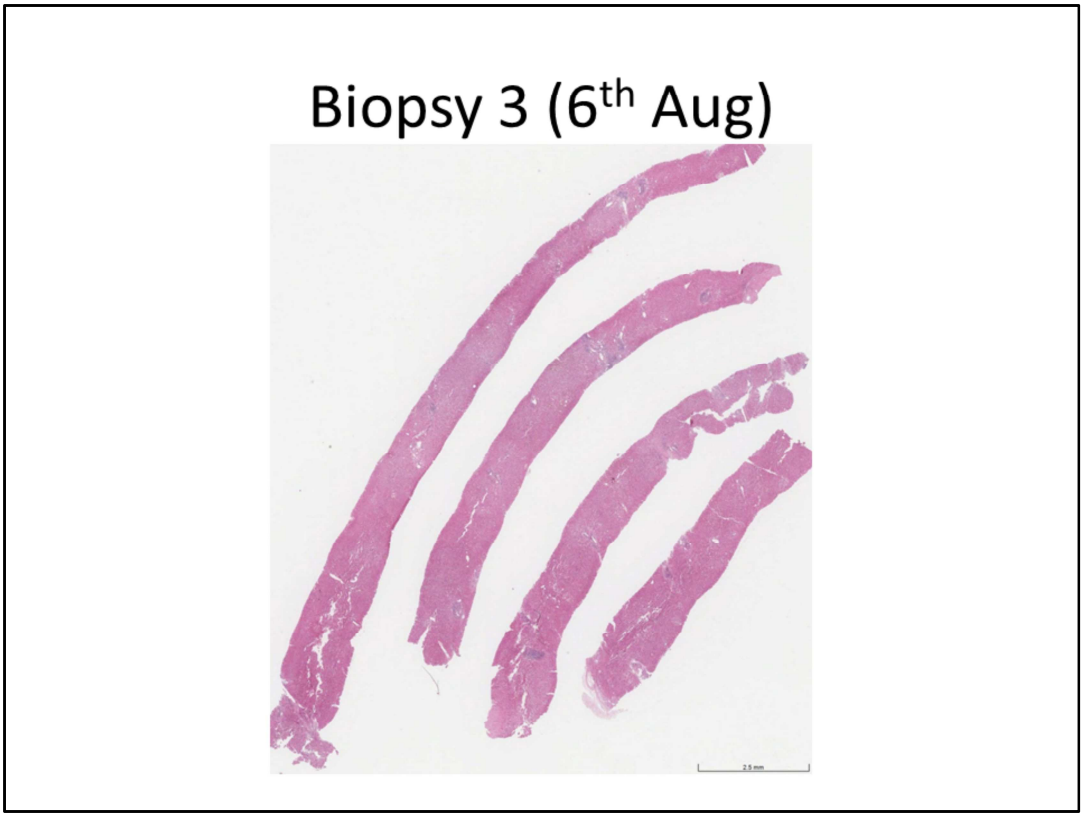
Bloods

	Bili	ALT	ALP	INR
03/08	376	541	560	1.1
04/08	436	606	-	1.3

Addenbrooke's bloods

06/08	507	802	917	

CRP 75
Renal function within normal limits
FBC NAD



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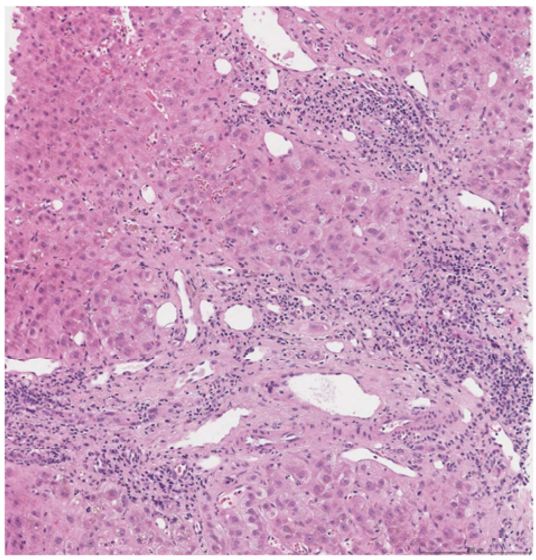
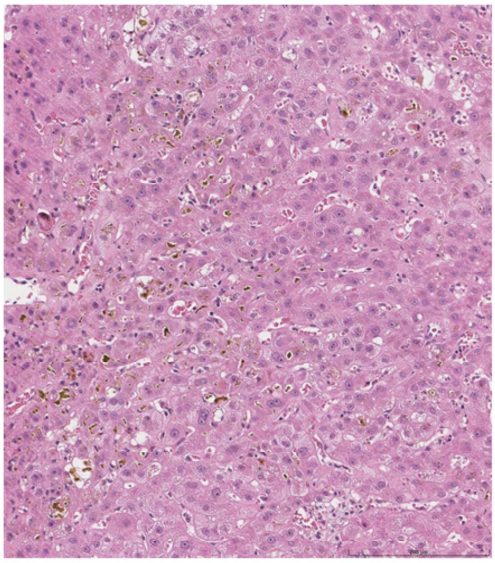
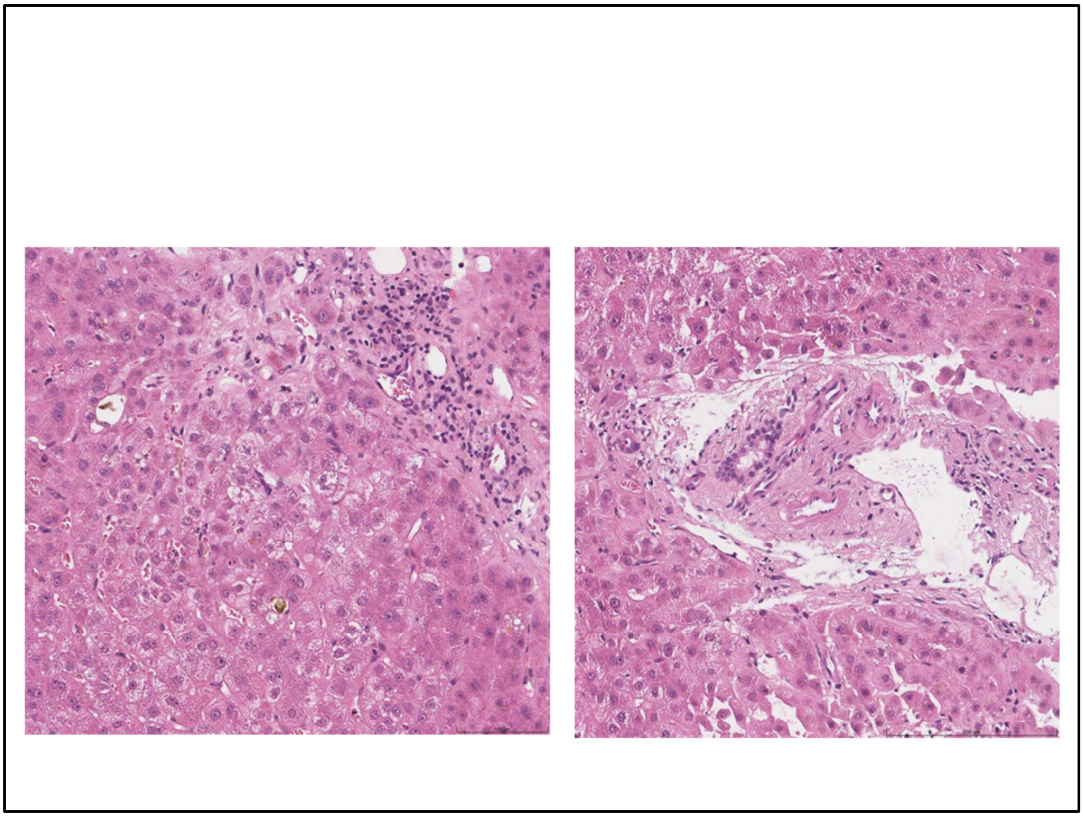
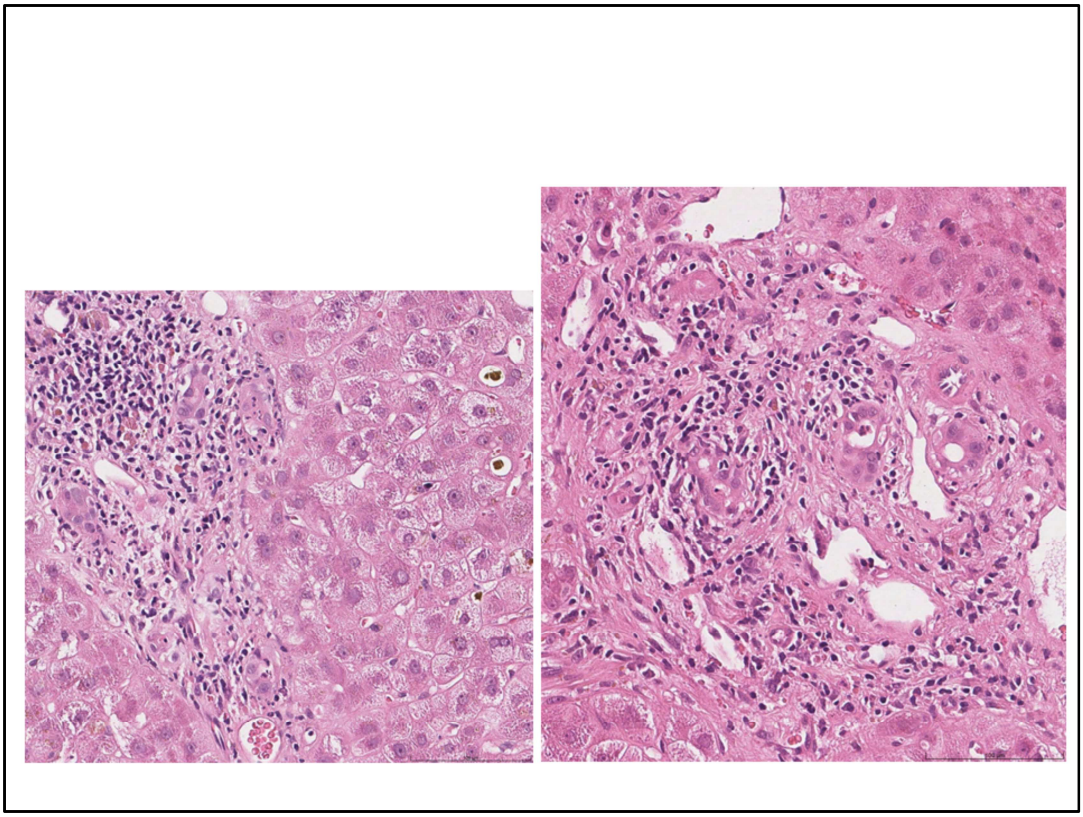
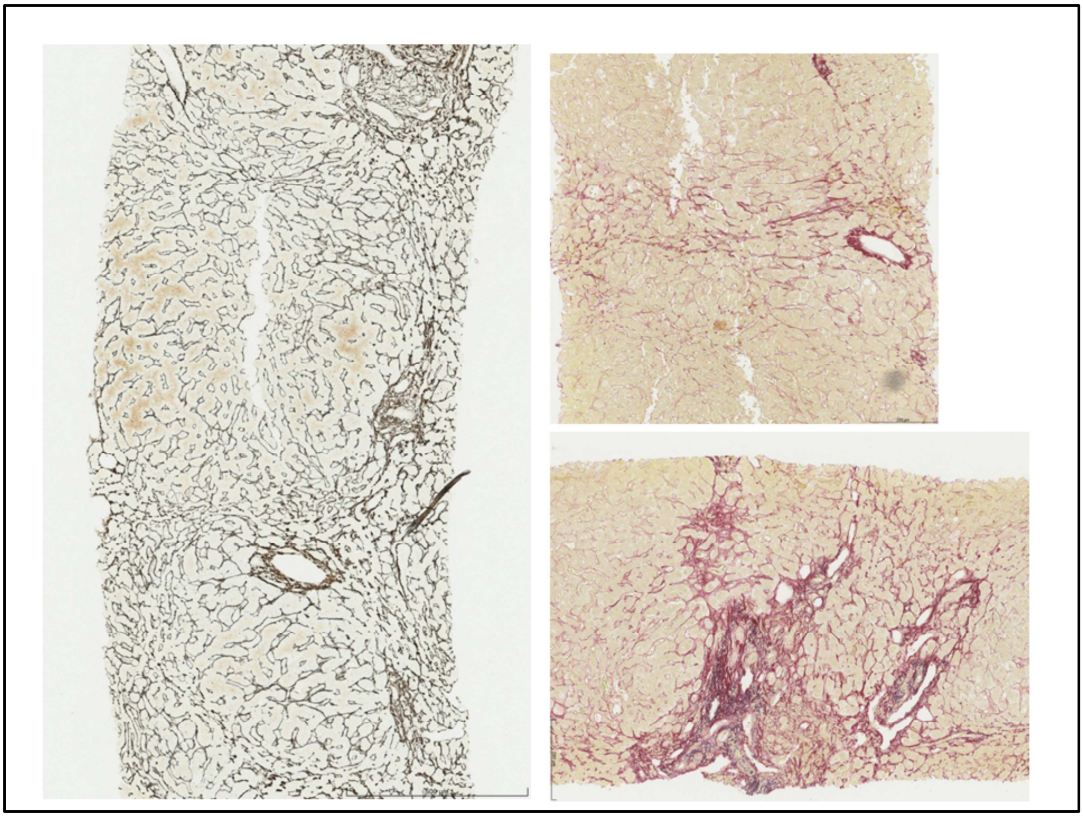






Mallory denk, variable portal change and duct atypia





Main findings

- Periportal fibrosis and distortion
- Portal inflammation - some improvement compared to biopsy 2
- Worsening cholestasis
- Severe degenerative duct atypia
- Focal cholangitis
- Focal duct loss
- No obvious ductular reaction
- Very minimal and focal copper deposition
- C4d immunohistochemistry negative

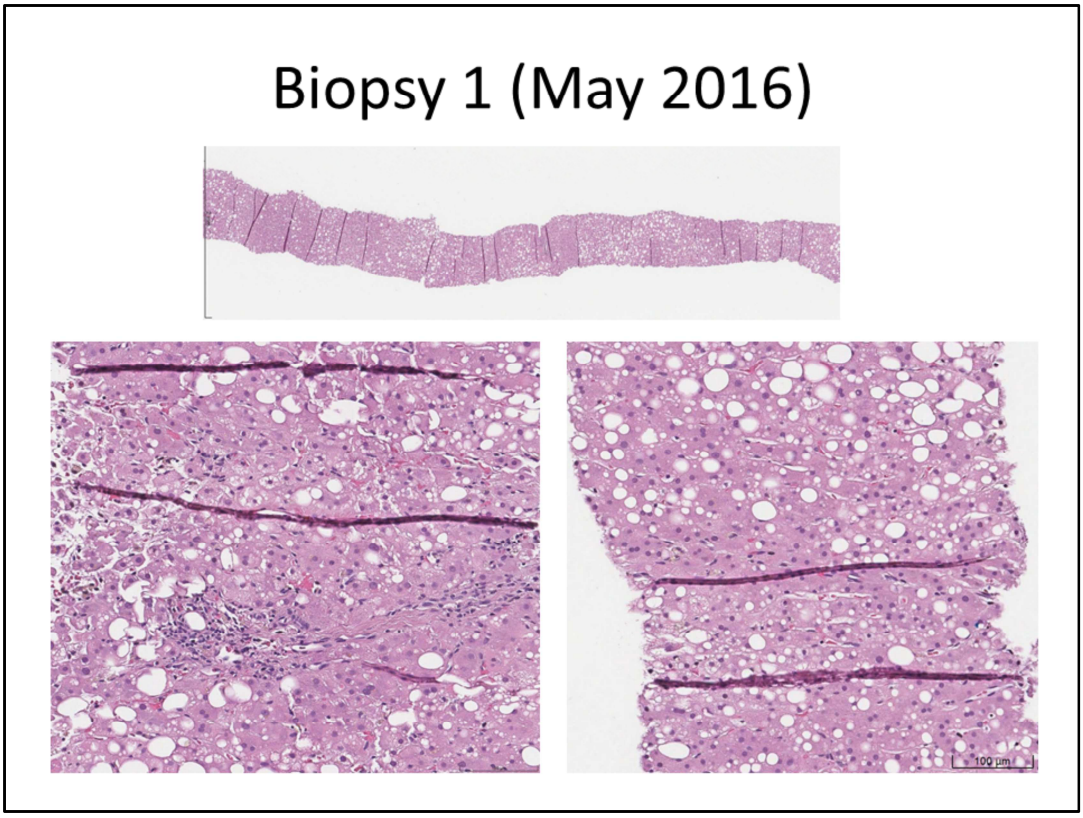
Liver graft biopsy, 2 years 9 months - there is subtle nodular regenerative hyperplasia-like architectural change, associated with prominent periportal fibrosis and distortion, with tiny Mallory-Denk bodies suggesting previous steatohepatitic injury may have been a contributory factor, although there is little residual steatosis. There is also a residual portal inflammatory infiltrate, less severe than in the recent biopsy (PQ17-04016), associated with severe degenerative duct atypia with focal cholangitis, but without significant ductular reaction or cholate stasis and with only focal ductopaenia. The degree of cholestasis appears excessive in comparison to the degree of duct injury and therefore raises the possibility of evolving chronic rejection.

Duct atypia similar to biopsy 2

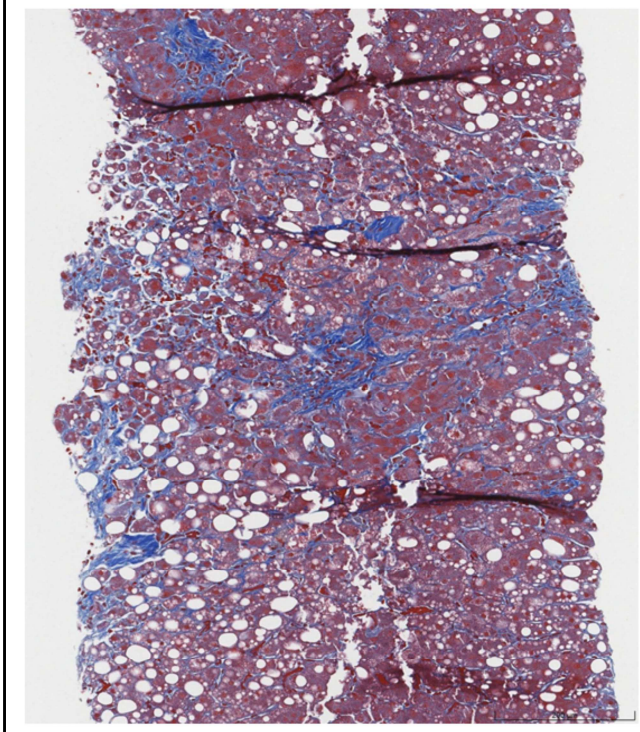
Progress

- Prophylactic antibiotics and antivirals
- Patent vasculature on triple phase CT
- MRCP
  - The liver is irregular in contour in comparison to imaging in 2014
  - The common duct is normal in calibre. There is, however, beading of the peripheral ducts in both right and left lobes. No intrahepatic duct dilatation
- Previously treated with azathioprine (stopped 2016)
- Obtain 2016 biopsy
- Treated as evolving chronic rejection

Repeat methylprednisolone and add in MMF mycophenolate



Outside slides, liver biopsy - moderate steatosis with borderline steatohepatitic activity and overall mild to moderate fibrosis. In addition there are subtle architectural changes suggestive of early nodular regenerative hyperplasia, but there are no features of rejection or ischaemia.



Progress

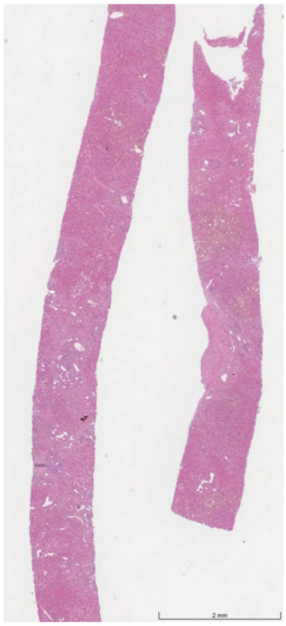
	Bili	ALT	ALP	CRP	
6/8	507	802	917		Addenbrooke's biopsy
8/8	577	791	1115	75	
10/8	531	516	1197		
14/8	517	673	1068	29	
17/8	489	539	1168	77	Gram –ve rods in BC
20/8	469	495	1664	110	Tazocin
25/8	378	382	1803	82	
30/8	383	341	1885	66	Further liver biopsy

Intermittent diarrhoea and lower abdo pain.
Albumin about 20 throughout.
Tazocin introduced and albumin slowly decreased from 20 to 16 from 20th Aug

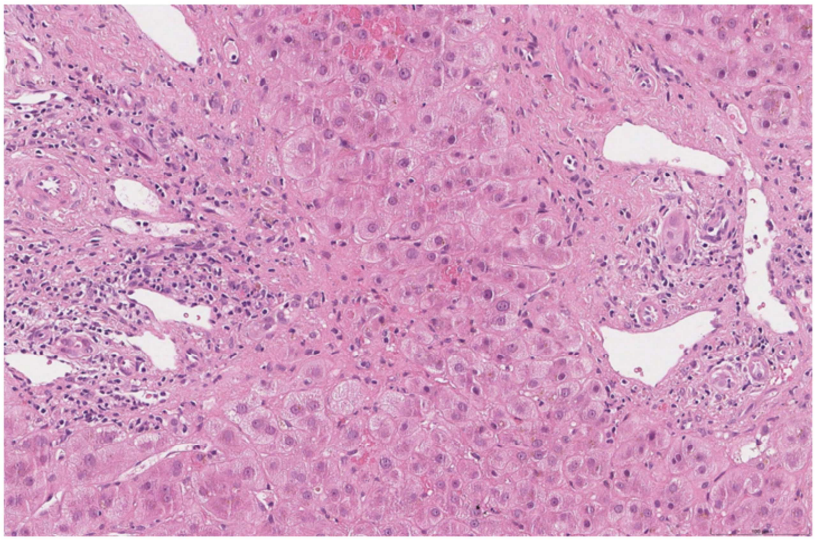
Further liver biopsy

- Mobilising with stick
- Being considered for re-transplant assessment
- Repeat biopsy
- ? Sepsis
- ? Progressive duct loss

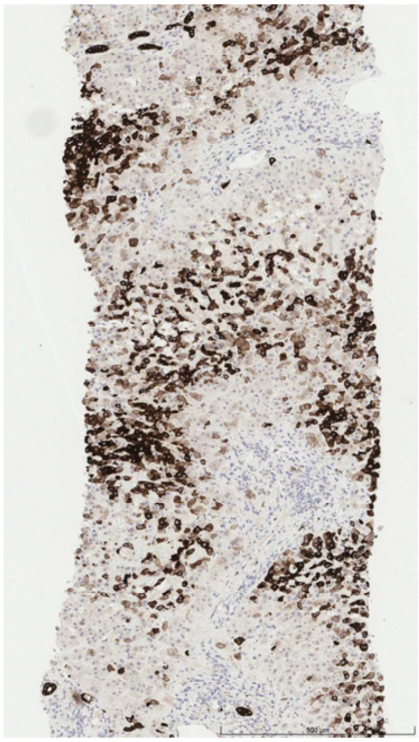
Biopsy 4 (30th Aug)

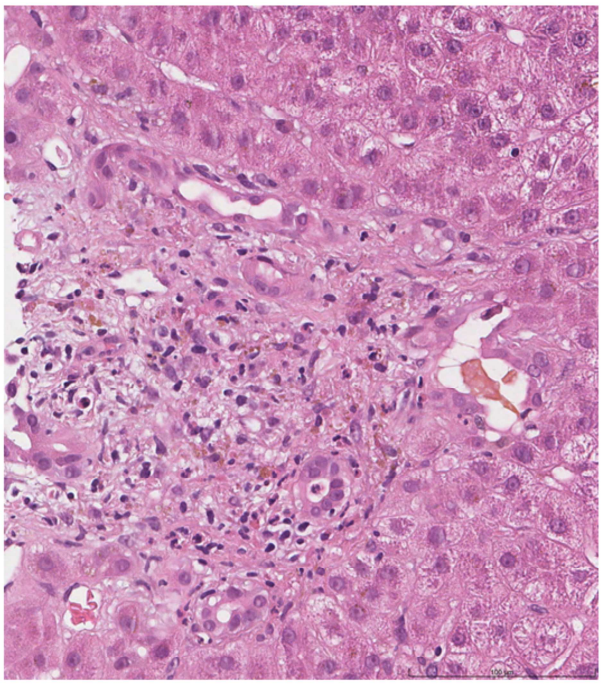


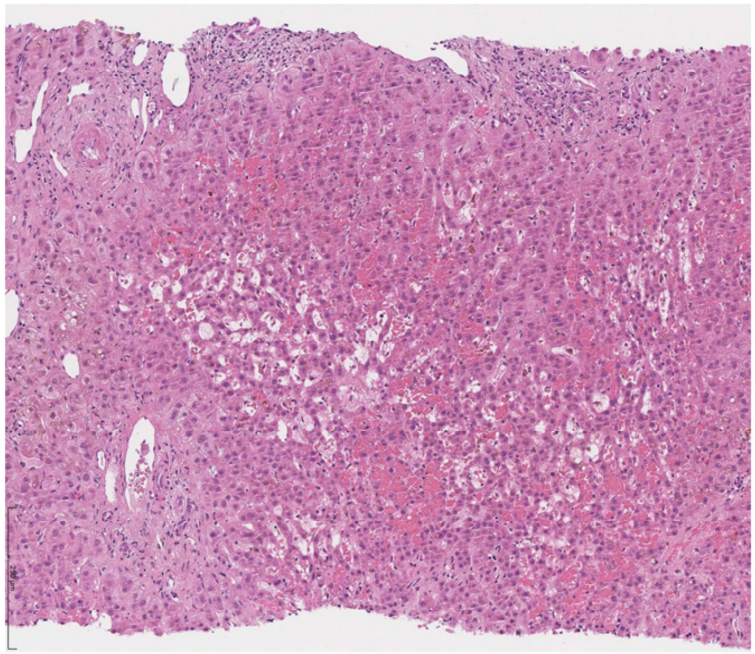
2 years 10 months

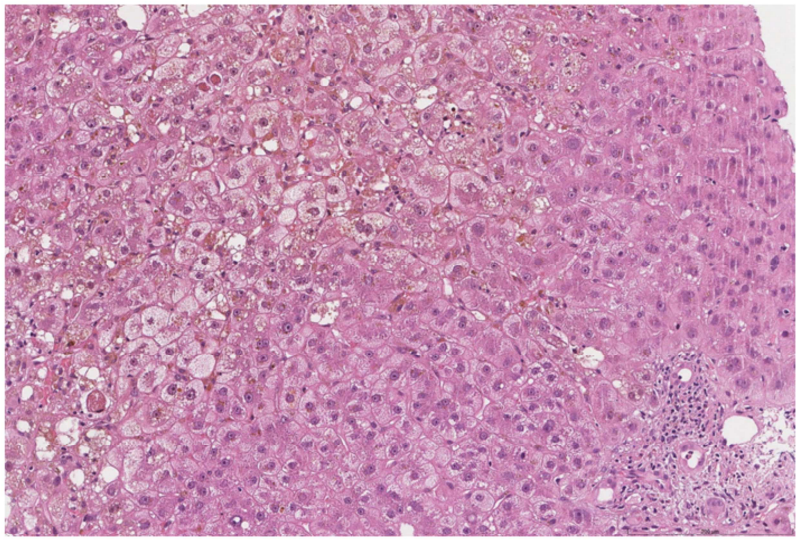


Globally worse duct atypia. Spectrum before but worse as a spectrum now..









Main findings

- Profound cholestasis
- Persistent portal infiltrate
- Worsening duct loss
- Venous outflow obstruction
- Features of sepsis

- Chronic rejection

Liver graft biopsy, 2 years 10 months - there are features suggestive of sepsis with underlying severe duct irregularity and atypia, focal ductopaenia and profound cholestasis implying evolving chronic rejection. There is a patchy and variable portal inflammatory infiltrate making comparison to the previous biopsy difficult, although the degree of overall inflammation appears slightly worse than in the previous biopsy (PS17-23671) with ongoing significant inflammation in a minority of tracts. The degree of duct irregularity, ductopaenia and cholestasis appears to have worsened slightly. Features of nodular regenerative hyperplasia persist, but in addition there are now also features suggestive of a degree of venous outflow obstruction.

? Meaningful to quantify duct loss

Progress

- 1/9 – rapid onset myalgia and proximal muscle weakness
- Absent reflexes, no sensory changes
- Stop atorvastatin and prednisolone
- Reduce MMF
- Increased CK and worsening myoglobinuria
- Treated as myopathy with rhabdomyolysis
- 5/9 – low level CMV viraemia

Cont....

	Bili	ALT	ALP	Total CK	
1/9	415	338	1842	1523	
5/9	462	298	1585	28092	AKI requiring RRT
7/9	586	471	1701	62302	
12/9	539	632	1478		Worsening RF

- 7/9 - worsening swallowing – NG tube placed
- Rapidly progressing subacute polymyopathy
- IV methylprednisolone
- 10/9 - worsening CMV viraemia
- 12/9 – multiple organ failure – palliative care

Likely related to atorvastatin.
Treated with IV methylpred in case autoimmune component.

Summary

- Chronic rejection
- Chronic hepatitis-like changes on initial biopsy
- Incomplete biochemical response to increased immunosuppression
- Ongoing infiltrate (patchy)
- Progressive bile duct atypia and loss
- Periportal fibrosis ? Previous rejection / NASH

- ? Compliance to immunosuppression

Relatively unusual features and presumably in early stages.

THANK YOU