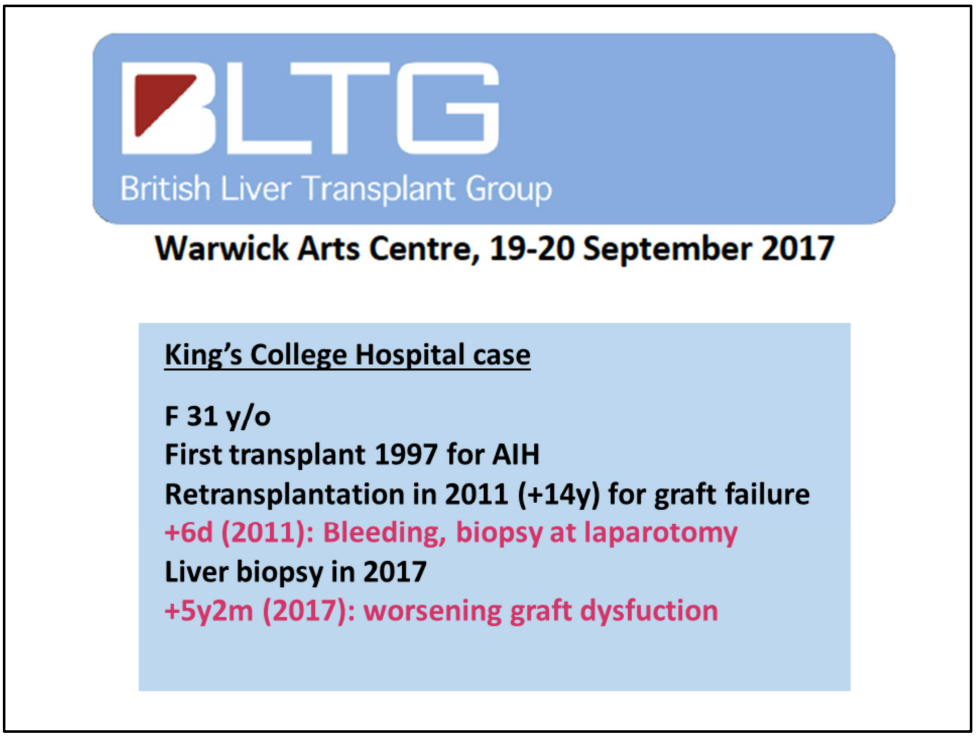
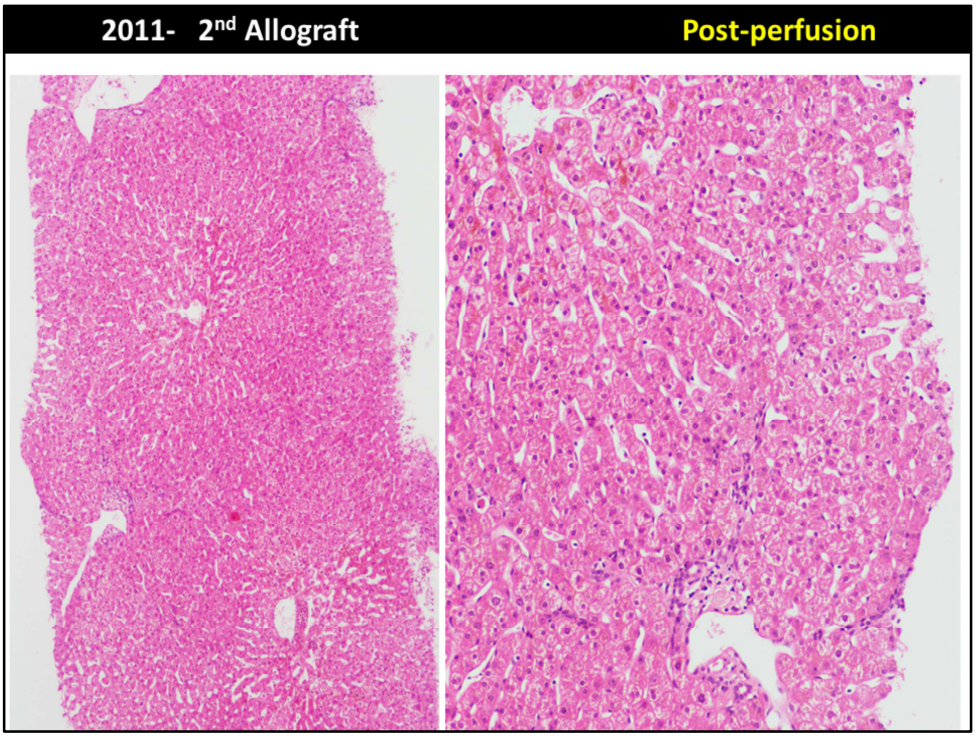
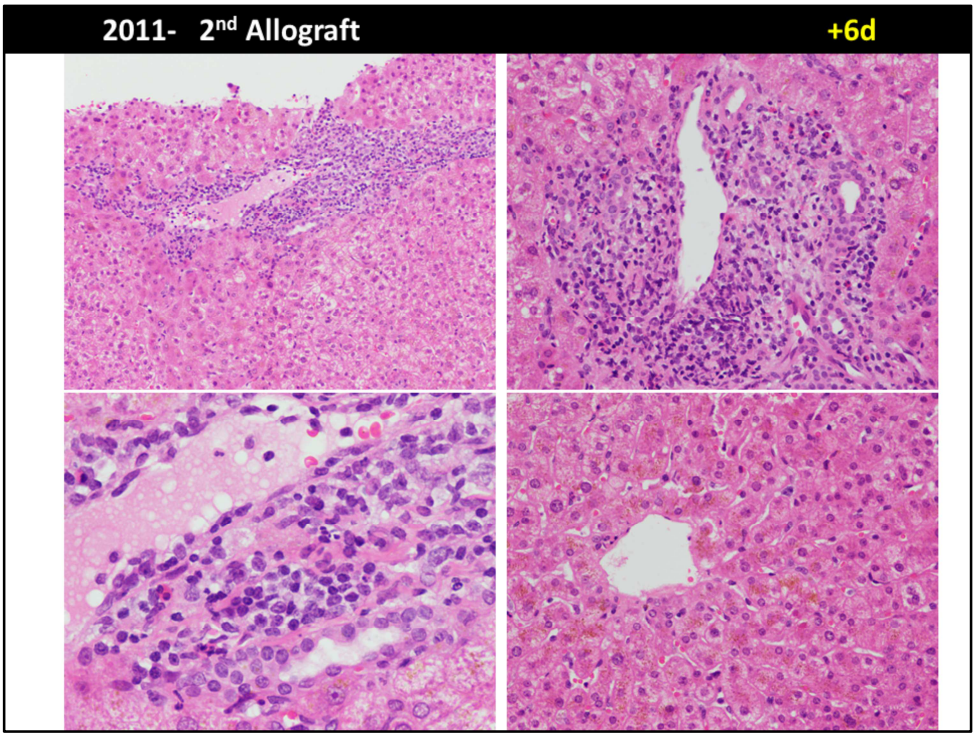


Good afternoon

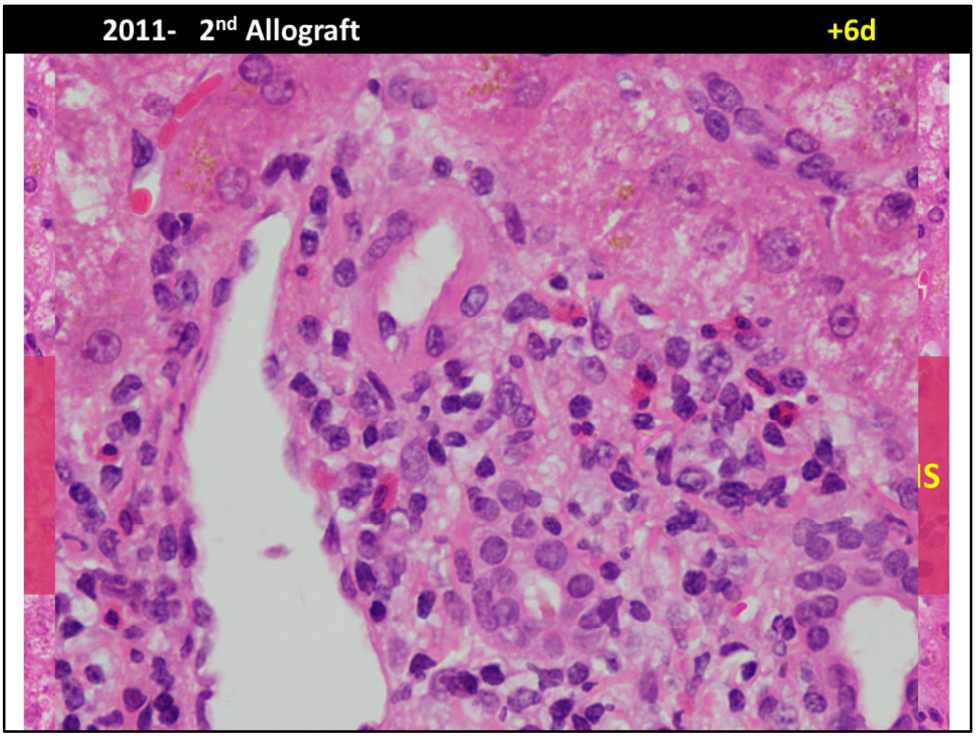
This case is from a young lady, frst transplanted in 97 for AIH, who was retransplanted for progressive graft failure 14 y after.
The only significant posttx event was an episode of bleeding for which a laparotomy was performed and a biopsy taken. After that she did not have clinically relevant findings until this year, when the biopsy I'm going to present was taken.



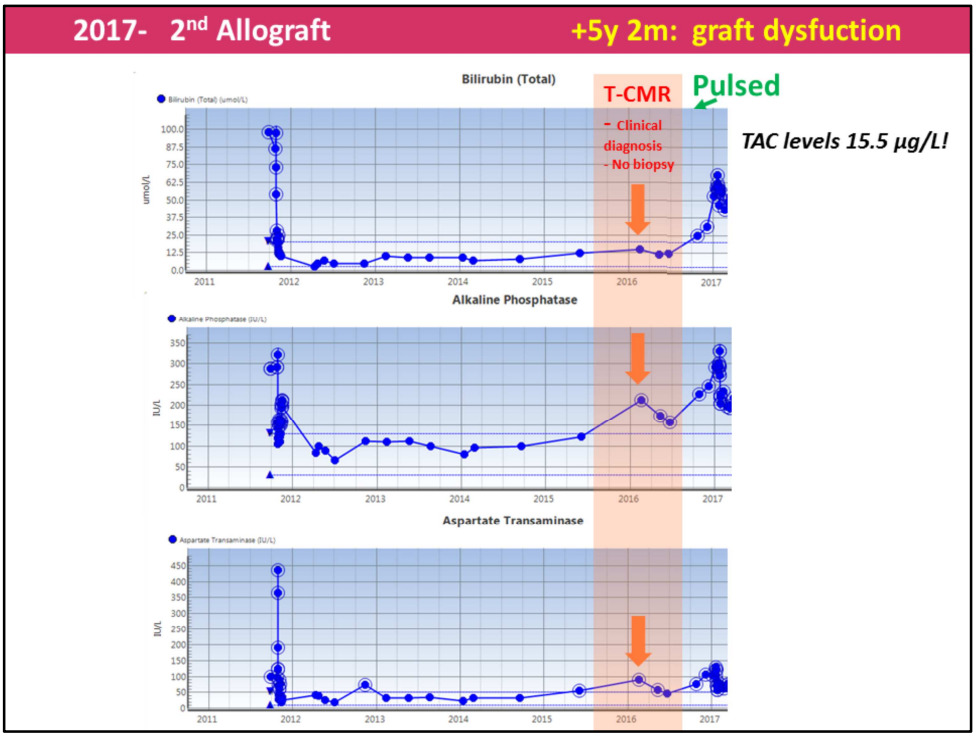
Just for completion a picture of the post-PF, with preserved vascular architecture and no abnormal histological findings



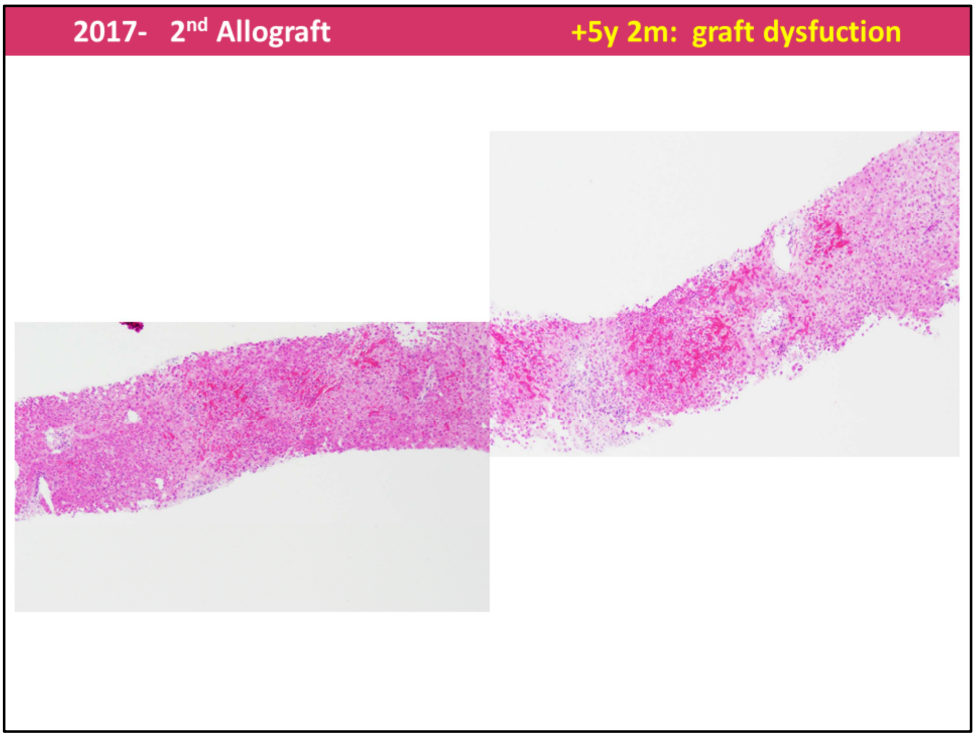
The biopsy taken during the lapartomomy for bleeding showed diffuse inflammatory portal enlargement, by mixed infamma infiltrate including eosinophils, small and large lymphs and occasional plasma cells. Bile duct damege was seen but minimal, non-destructive. Portal vein endotheliitis was significant and CL areas and CV did not show PV or endothelitis or hepatocellular changes (no features of ischaemia)



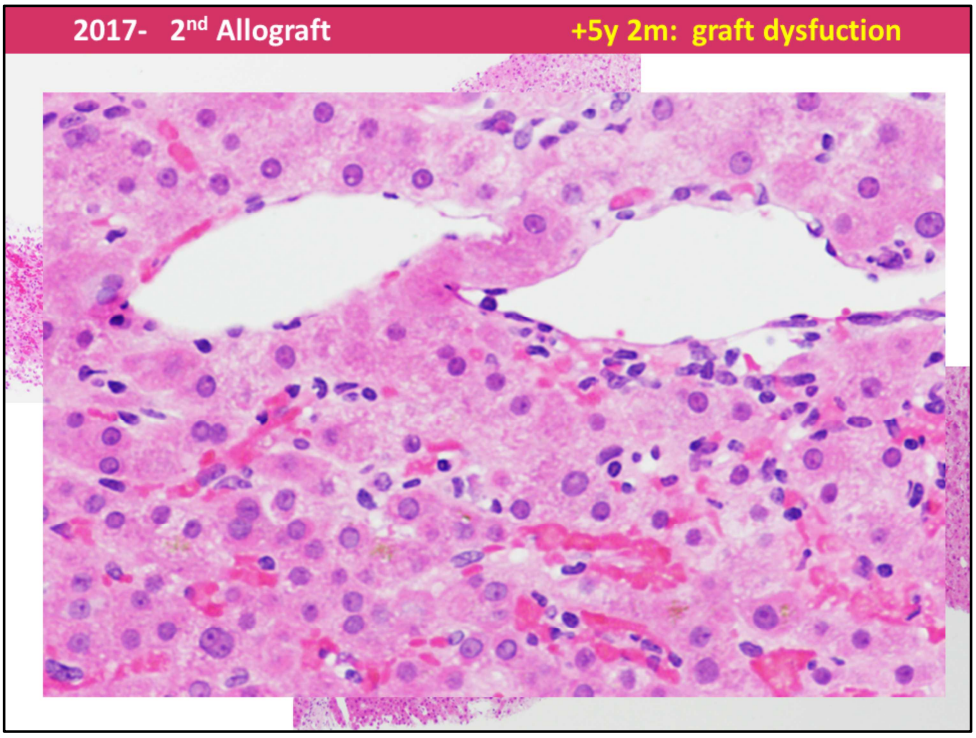
With these findings the diagnosis was moderate ACR, that was treated with intensification of the baseline IS and followed by improvement of the LFTs.



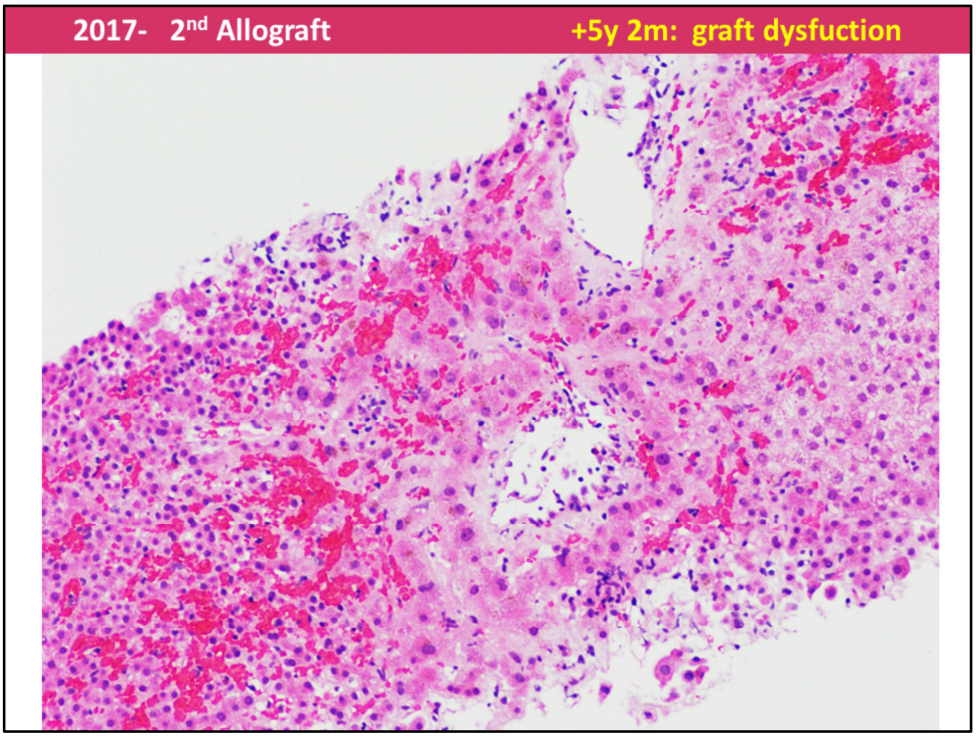
From that episode the clinical course was unremarkavble as you can observed in these graphics from the end of 2011 after the retransplantation until 2017. In 2016, an increase on the cholestatic and transaminases enzymes was detected, clinically interpreted as ACR and the patient pulsed with steroids, without a liver biopsy. Just a comment on presence of high levels of TAC at that point.
From that time there was a progressive increase of the cholestatic enzymes, transaminases and bilirrubin, and our current biopsy was taken



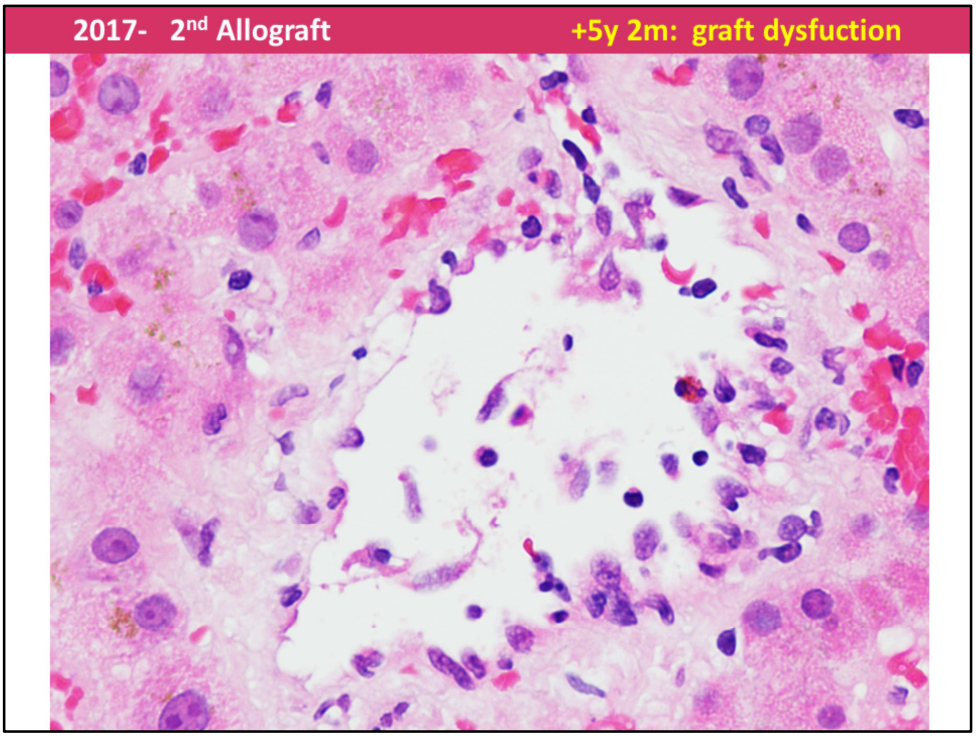
At low magnification the biopsy showed heterogeneous staining, with these red congestive areas



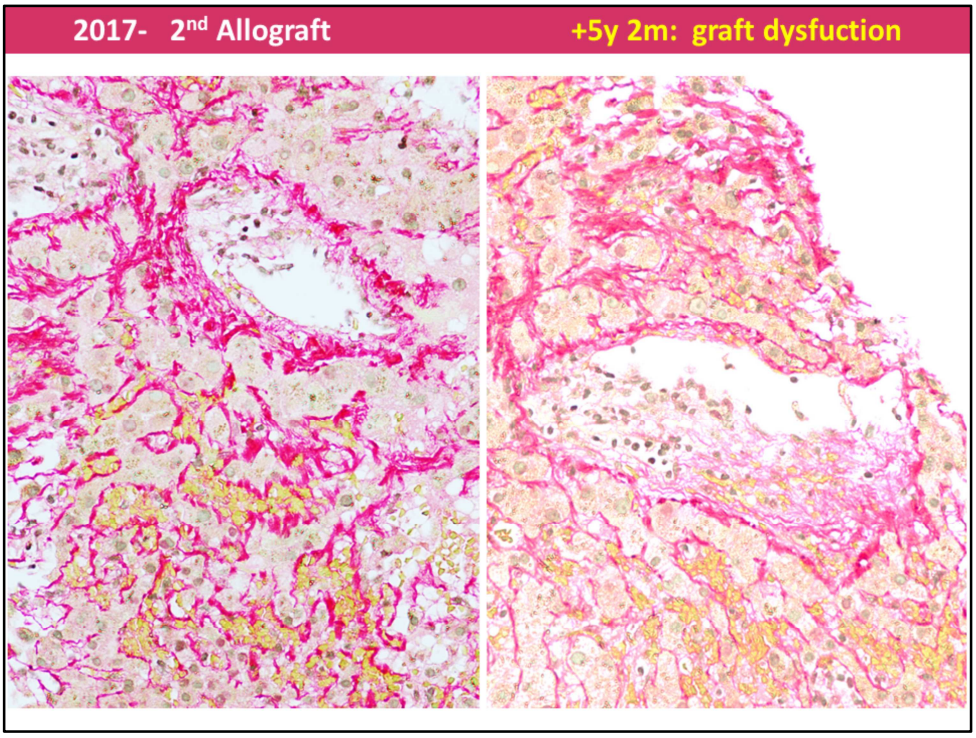
As well as zones of portal inflammation



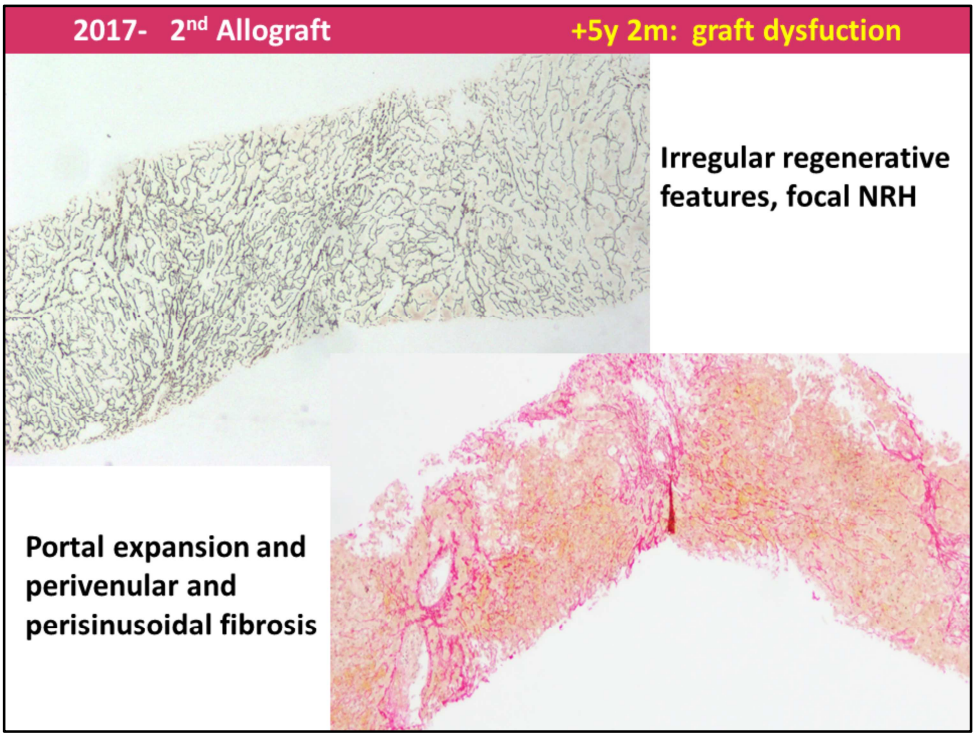
The most remarkable changes were at the centrilobular and midlobular areas, with presence of brisk sinusoidal congestion, liver plates atrophy, and presence of endothelial damage in most CVs, with proninent endothelia and endothelitis



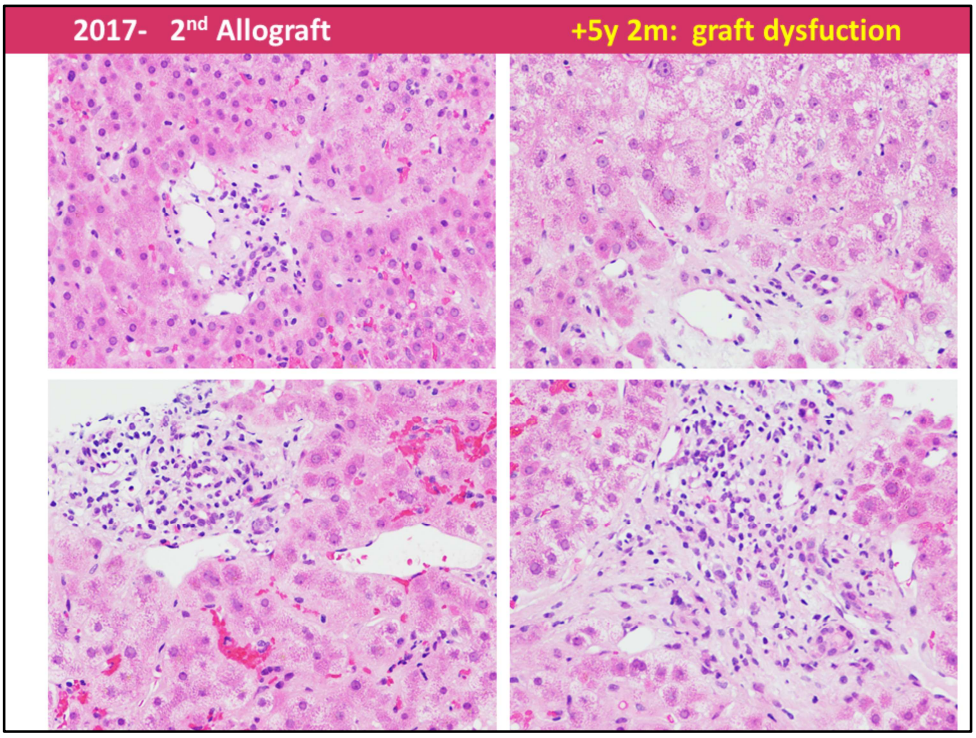
As you can see in more detail, with presence of occasional eosinophils in that infiltrate



Sirius red for collagen fibres demonstrates irregular fibrous thickening of the CV wall, with focal early loose fibro-obliterative lesions
And prominent perisinusoidal fibrosis

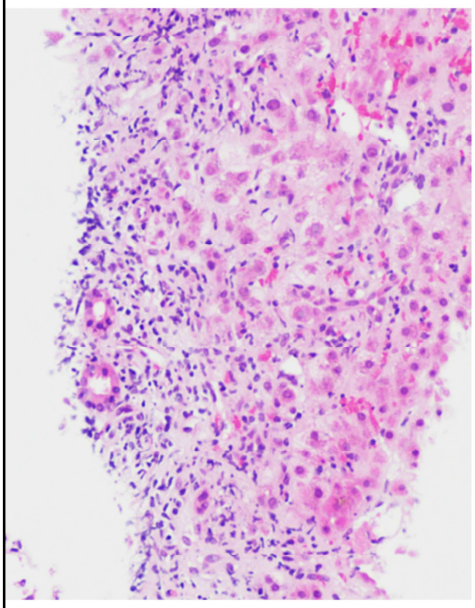


The architecture was clearly abnormal, with reticulin stain showing irregular regeneratibe changes (focal NRH)
Portal tracts were also expanded

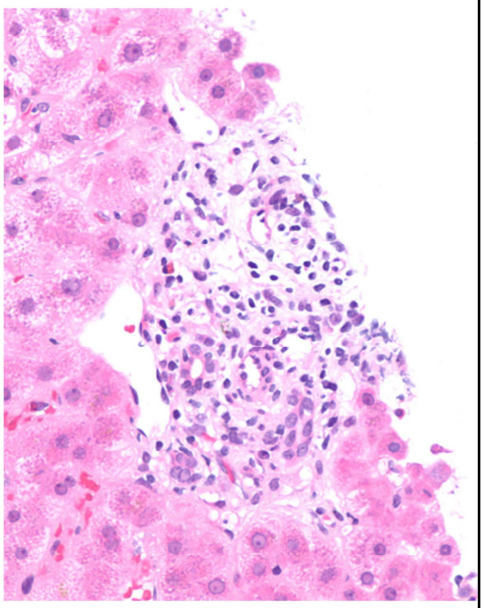


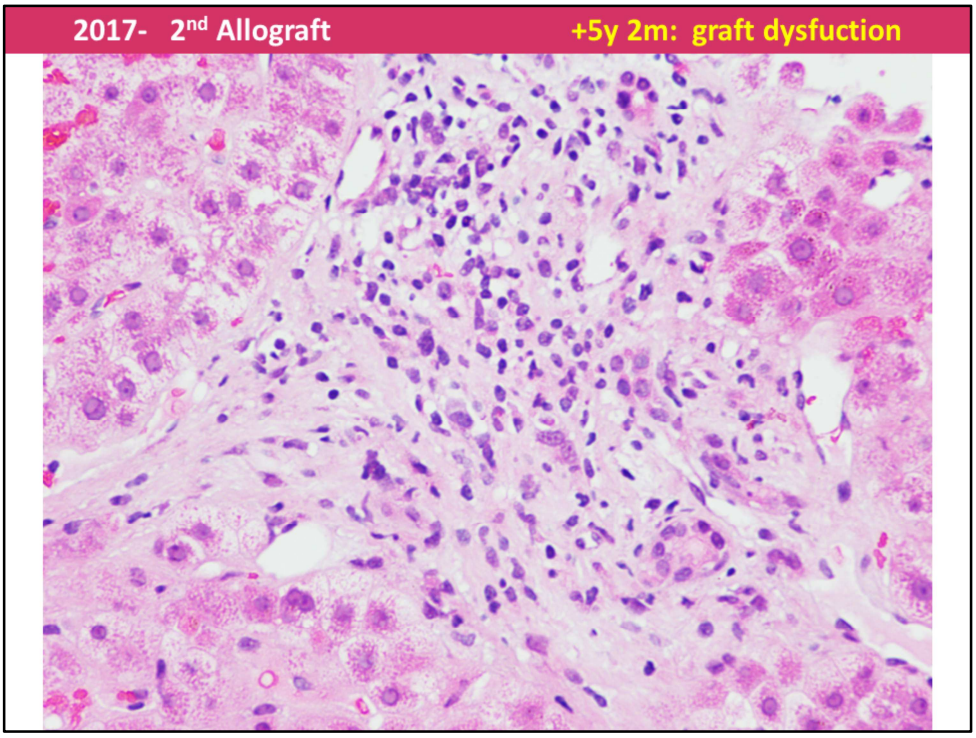
Portal inflammation was variable, with occasional portal tracts with minimal changes, but most of them showed an overall mild inflammatory component with lymphs and occasional palsma cells. As you can see in the images bile ducts were preserved,with minimal epithelial damage, and ductular reaction was not a feature. Interface hepatitis in not significant if any.
Of note are also de abnormal portal microvasculature, with absence or attenuation of most portal vein branches and the identification of these small paraportal thin-walled structures, dilated, features similar to those found in biopsies with portal hypertension.

2017- 2nd Allograft

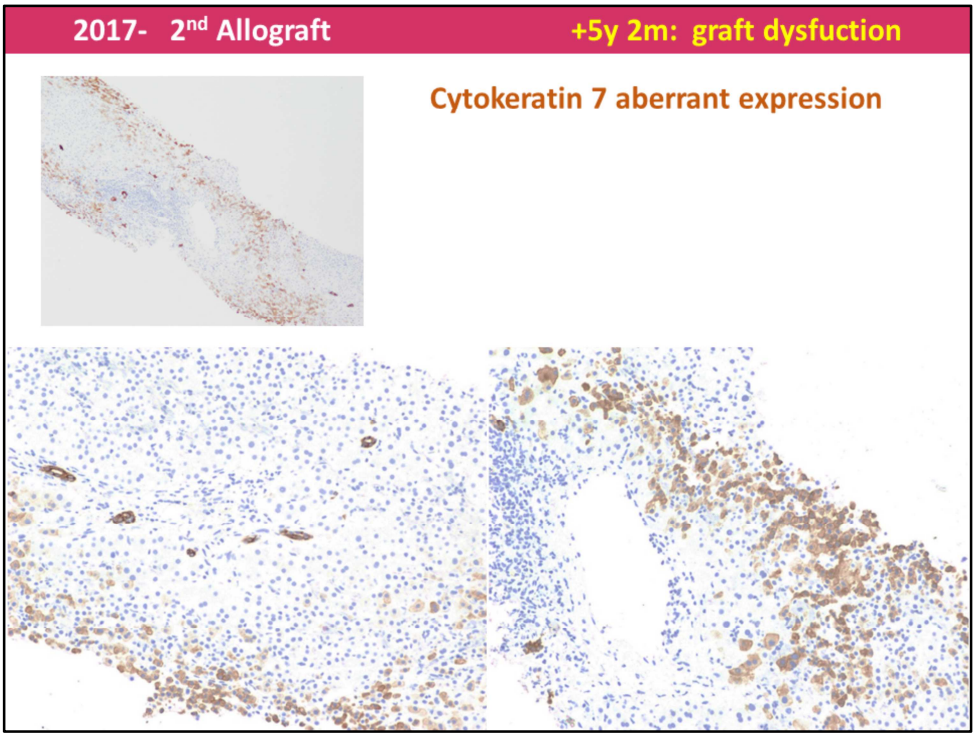


+5y 2m: graft dysfuction

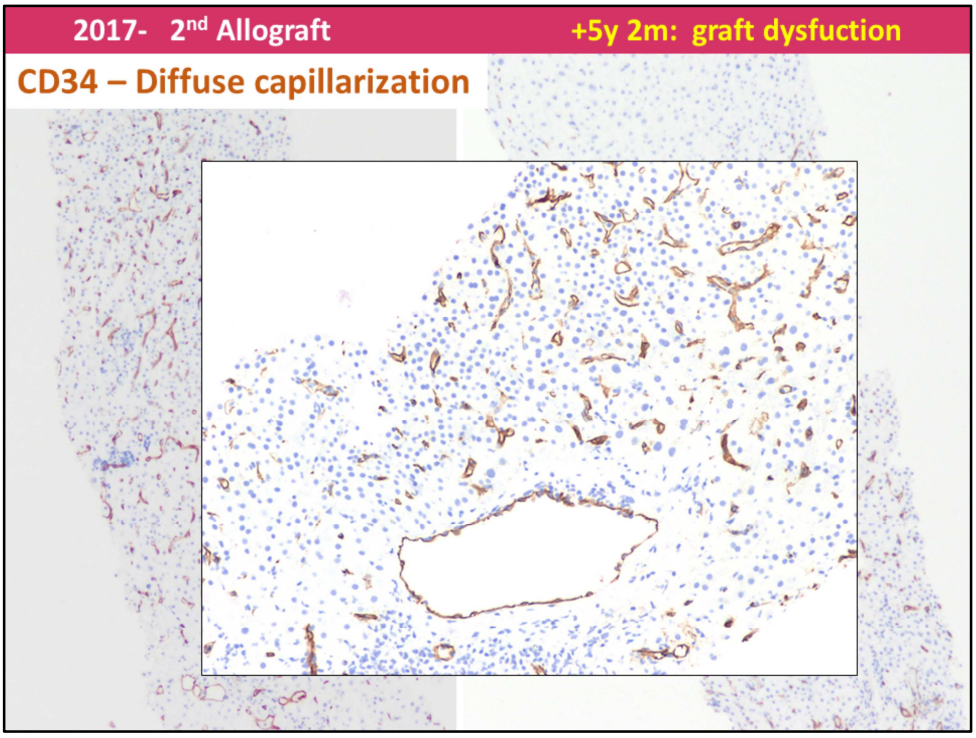




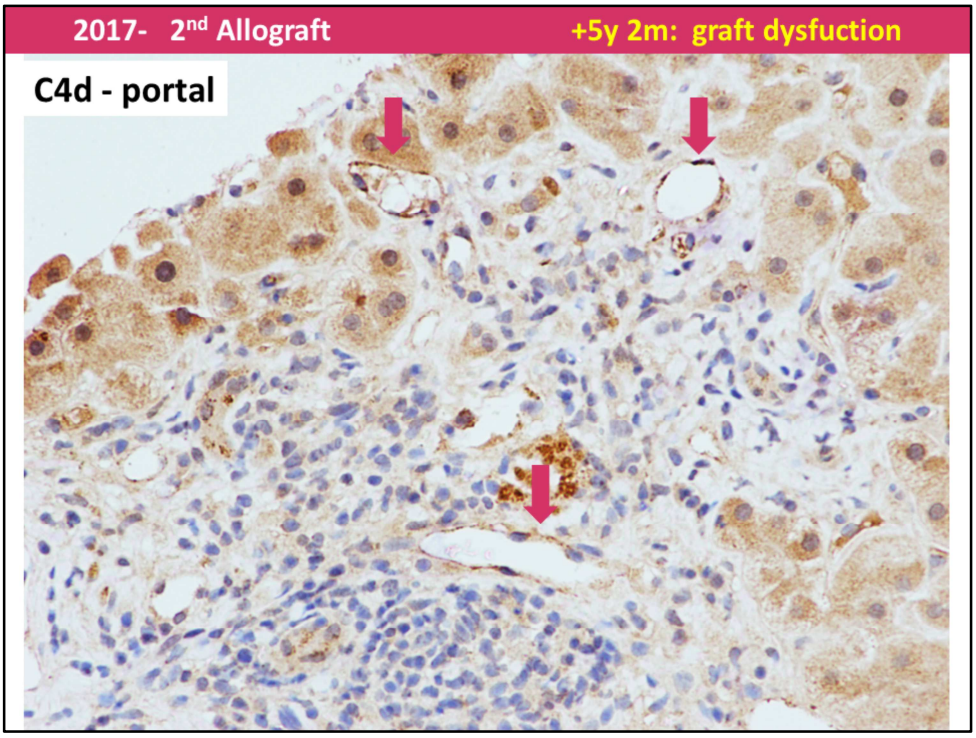
No capillaritis



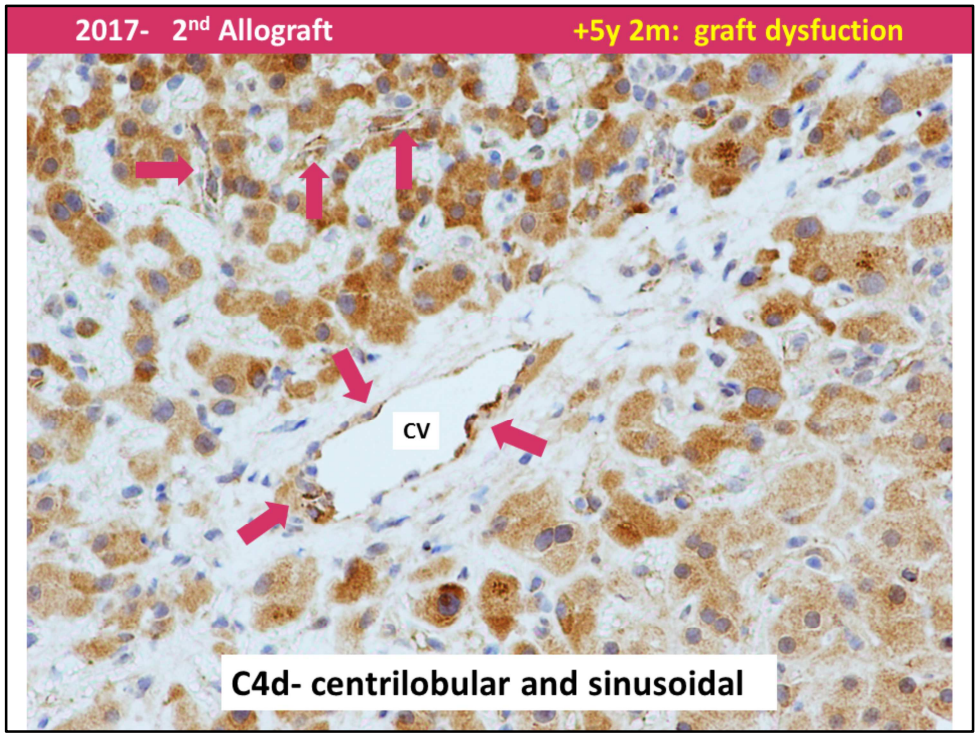
No capillaritis



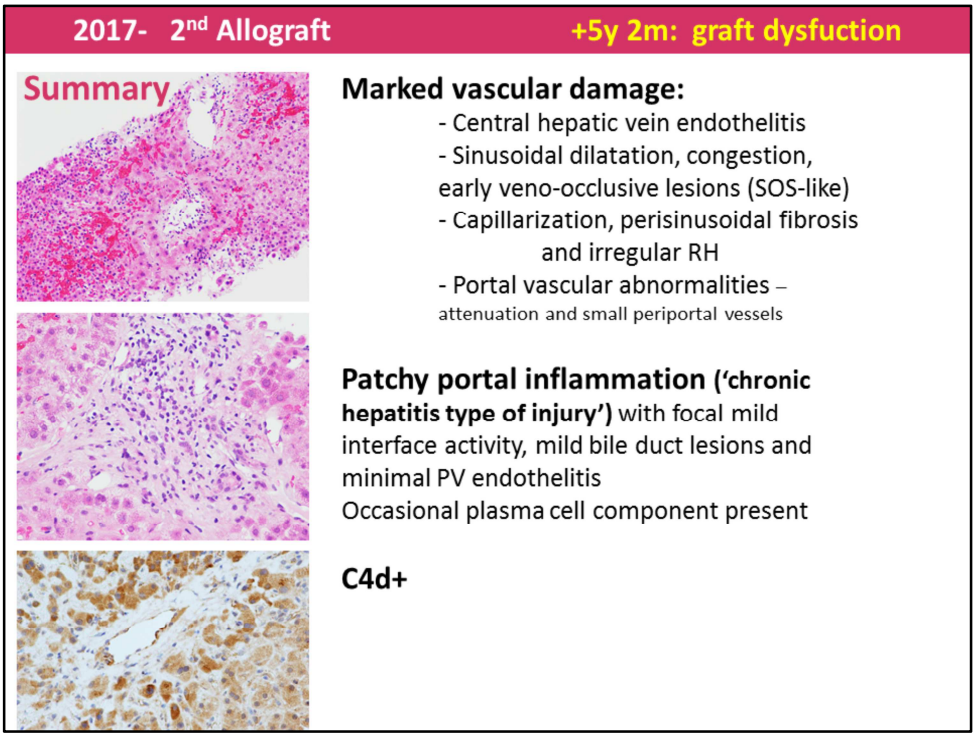
CD34 is in keeping with the abnormal hepatic vascularization (arterialization) with extensive diffuse pattern



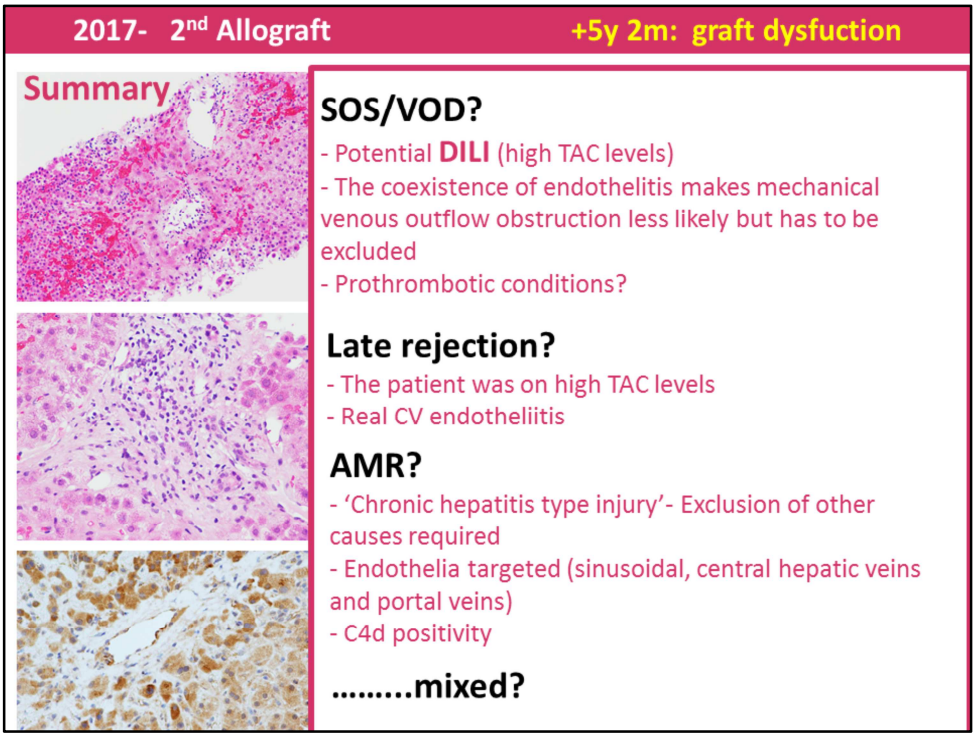
And finally C4d staining, (techically not the best, with strong background, but confident endothelial stain) that was positive at the portal areas



And sinusoids and CV endothelia



So in summary we have a chronic allograft damage with two main features: marked patchy vascular lesions and portal inflammation.
The vascular damage involves all the vascular compartments of the liver, sinusoids, CVs and PVs, in different degree and features. SOS like features are present, with sinusoidal dilatation, acute congestion and veno-occlusive lesions.



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Meeting Report

2016 Comprehensive Update of the Banff Working Group on Liver Allograft Pathology: Introduction of Antibody-Mediated Rejection

A. J. Demetris, C. Bellamy , S. G. Hübscher et al.

Table 7: Criteria for chronic active liver allograft AMR

Probable chronic active AMR (all four criteria are required):

(1) Histopathological pattern of injury consistent with chronic AMR: both required:
   (a) Otherwise unexplained and at least mild mononuclear portal and/or perivenular inflammation with interface and/or perivenular necro-inflammatory activity (Figures 4 and 5).[1]
   (b) At least moderate portal/periportal, sinusoidal and/or perivenular fibrosis.[2]
(2) Recent (for example, measured within 3 months of biopsy) circulating HLA DSA in serum samples;
(3) At least focal C4d-positive (>10% portal tract microvascular endothelia) (Figure 5).
(4) Reasonable exclusion of other insults that might cause a similar pattern of injury (see text).

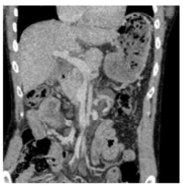
Possible chronic active AMR:

(1) As above, but C4d staining is minimal or absent

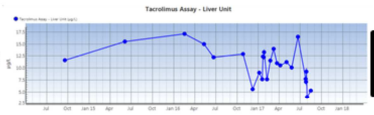
ADCC, antibody-dependent cellular cytotoxicity; AMR, antibody-mediated rejection; DSA, donor-specific antibodies; HLA, human leukocyte antigen; TCMR, T cell–mediated rejection.
[1]It is difficult, at this time, to determine whether the mononuclear infiltrates are related to AMR (e.g. ADCC with capillaritis) or TCMR (mostly T effectors cells) or mixed AMR and TCMR. More research is needed on this topic.
[2]CD34 and SMA stains might be considered to study sinusoidal capillarization and stellate cell activation.

With all these findings features are highly suggestive of cAMR

Additional clinical information



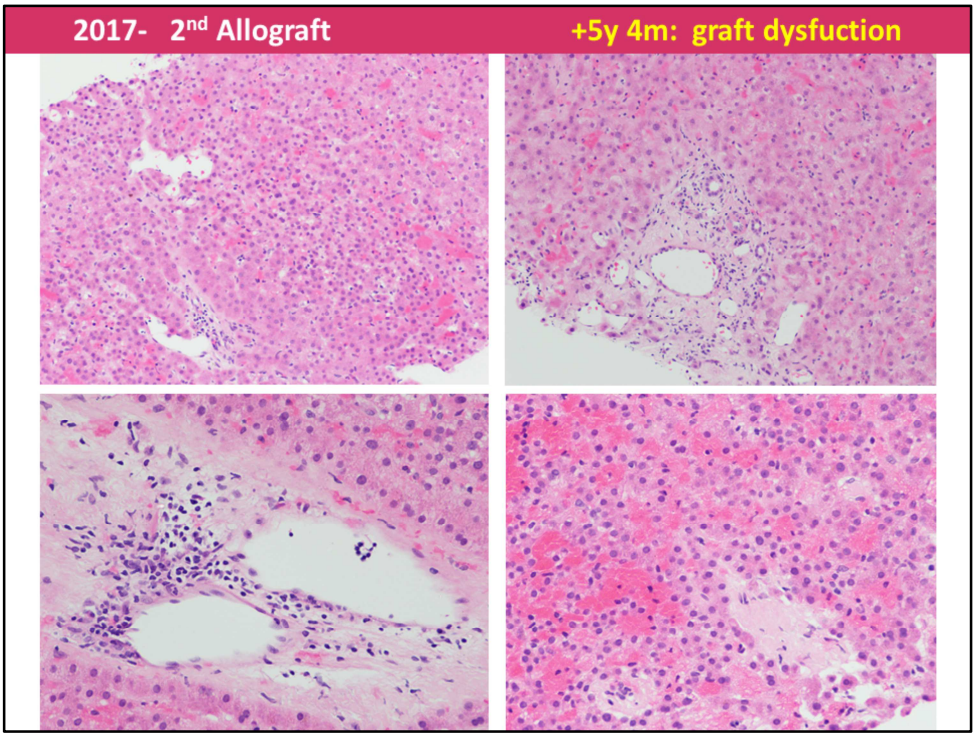
- **Imaging studies**:
  No vascular compromise
  Negative
- **Serology and procoagulant status**:
  Negative
- **Other**:
  Tacrolimus
  15.5 µg/L



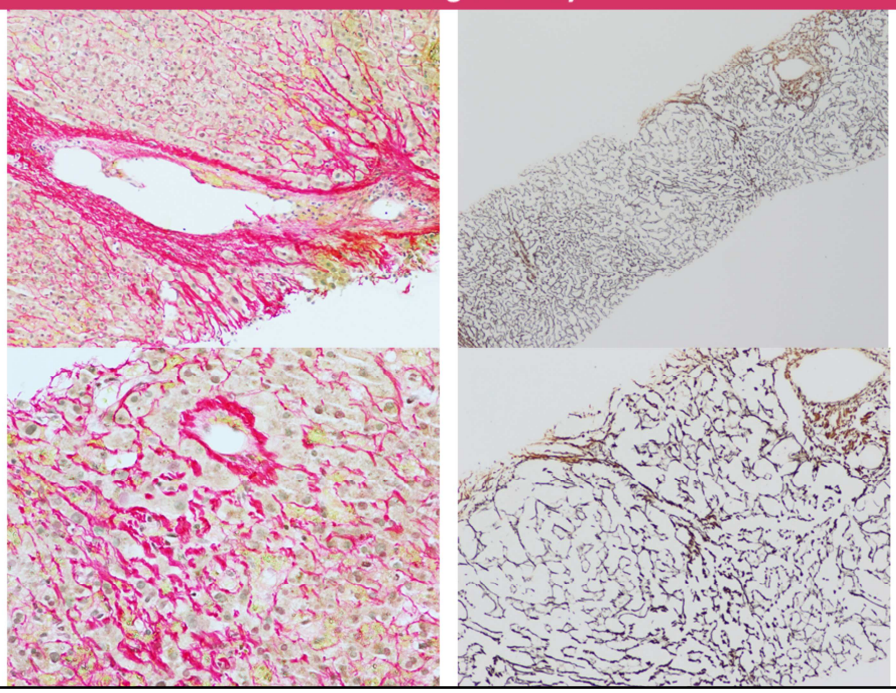
← Control

Treatment:
Triple IS: Advagraf + MMF + Prednisolone

- Clinically and serologically not improving
- After 2 m from the previous biopsy:
  weight gain and ascites


2017- 2nd Allograft
+5y 4m: graft dysfuction

2017- 2nd Allograft +5y 4m



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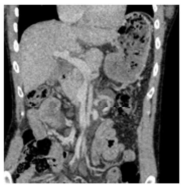

- **Serology**:
  Negative

- **Other**:
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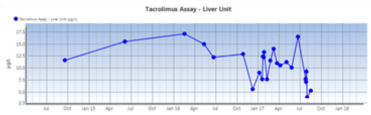
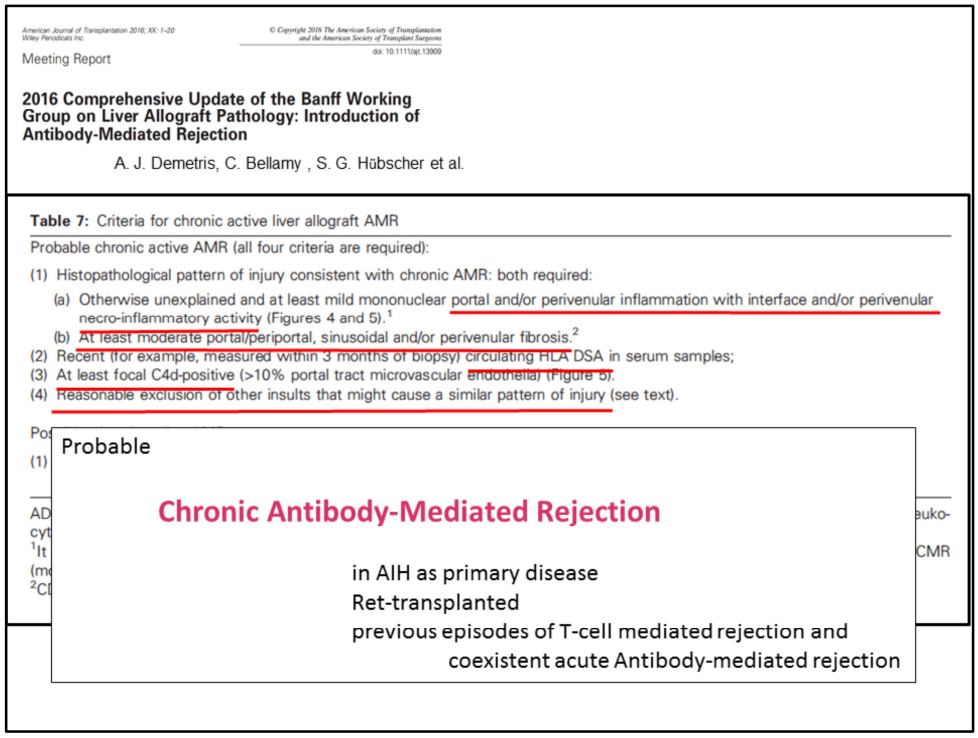


- **DSA class I and class II**
  Positive
  MFI: 10.559



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Probable

Chronic Antibody-Mediated Rejection

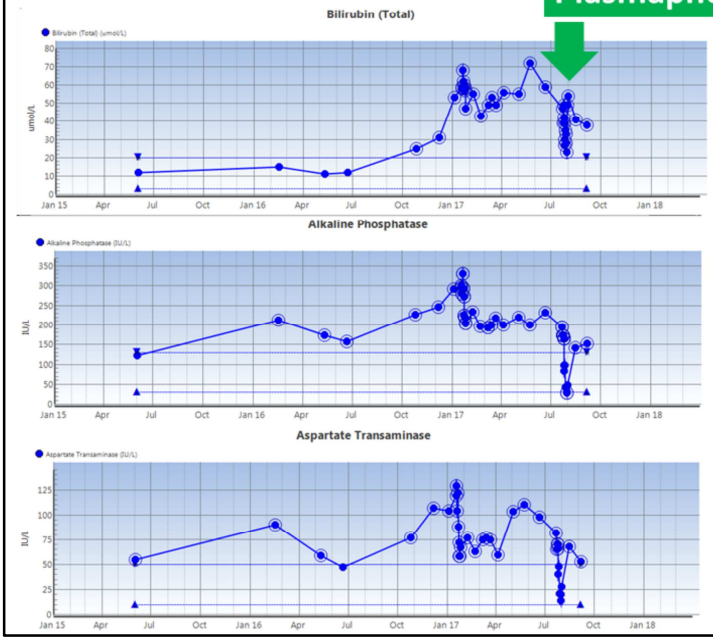
in AIH as primary disease
Ret-transplanted
previous episodes of T-cell mediated rejection and
coexistent acute Antibody-mediated rejection

With all these findings features are highly suggestive of cAMR

2017- 2nd Allograft

+5y 2m: graft dysfuction

Plasmapheresis (25-30/7/17)



LFTs 5/9/17

ALB: 33

AST: 53 IU/L
BIL: 38 umol/L
GGT: 194 IU/L
ALP: 153 IU/L

PLT: 181 10^9/L

Discussion points

Peculiar histology: SOS/VOD-like

Differential diagnosis

- Mechanical venous outflow obstruction
- Pro-thrombotic condition
- DILI (?TAC)
- AMR

Long interval of normality (2011-2016) and relatively 'abrupt' onset

? Precipitating factors (?TAC)

?Outcome of this patient

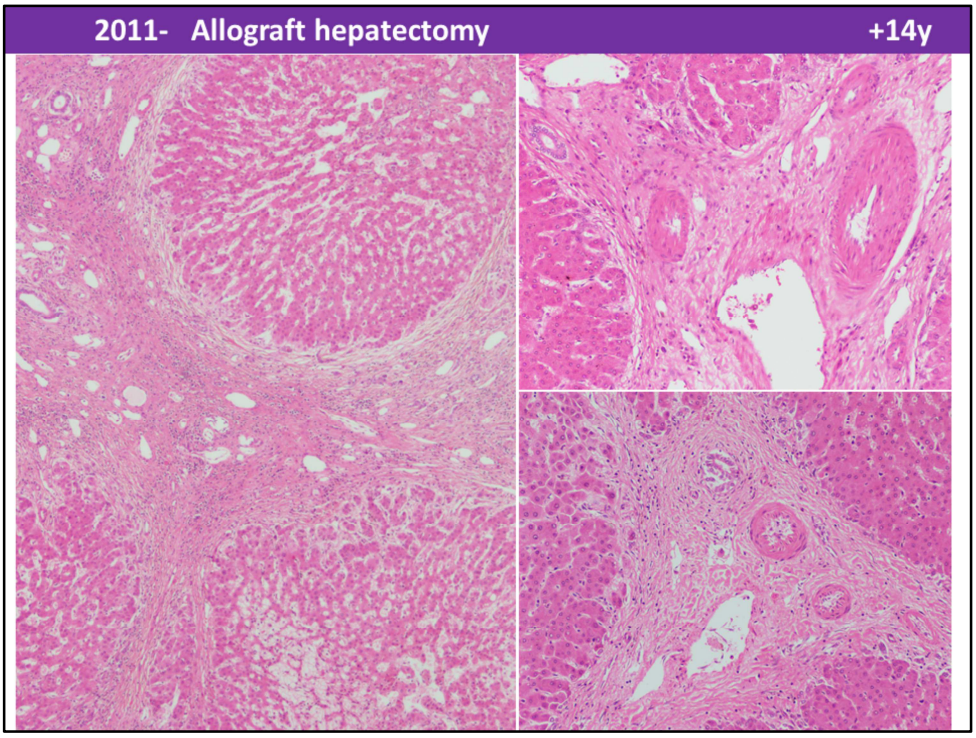
High score on proposed cAMR score

First transplant 1997 for AIH
Retransplantation in 2011 (+14y) for graft dysfunction

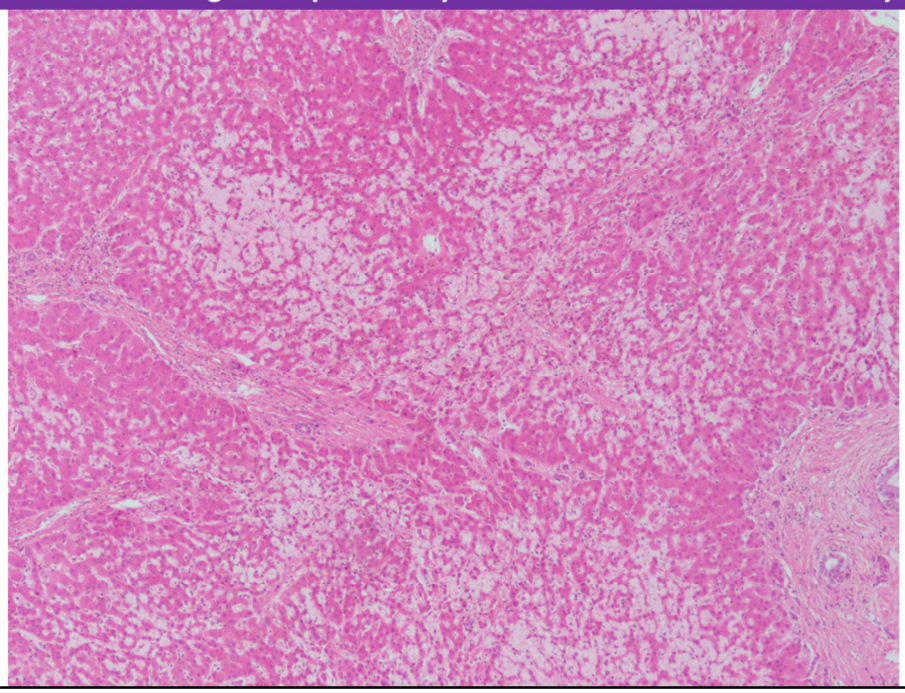
+12y

Abnormal LFTs
(AST 200, Bil 39, GGT 291, AlkP 584)

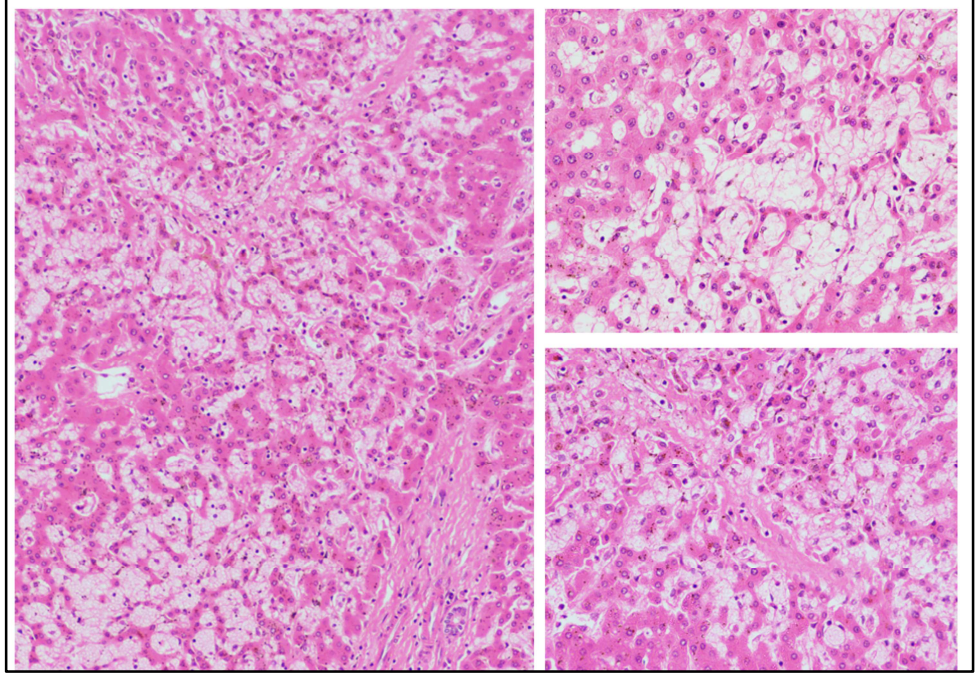
?recurrent AIH
?rejection
?Cholangiopathy


2011- Allograft hepatectomy
+14y

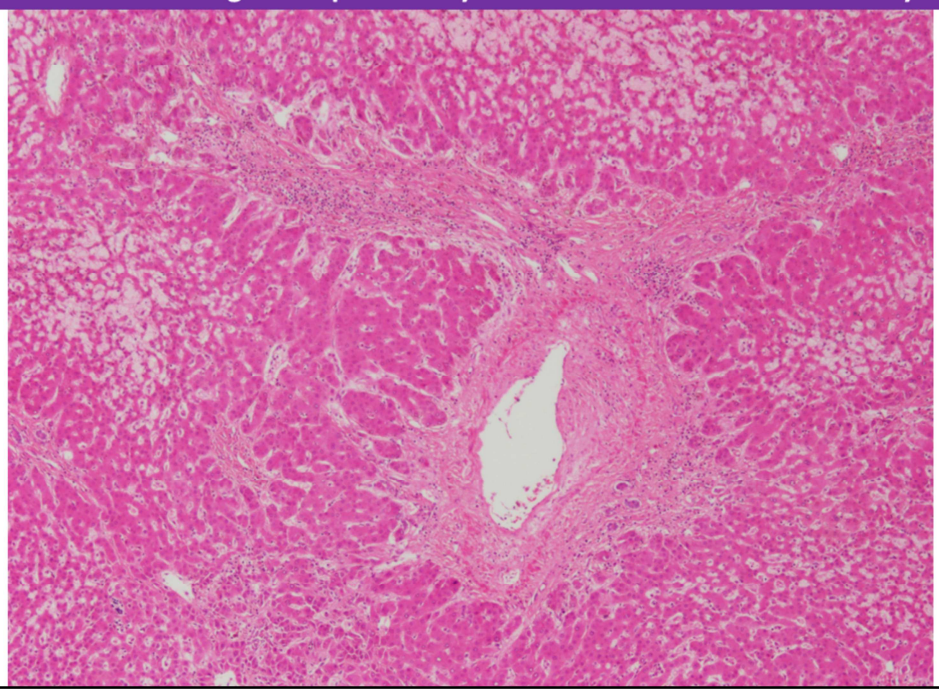
2011- Allograft hepatectomy +14y



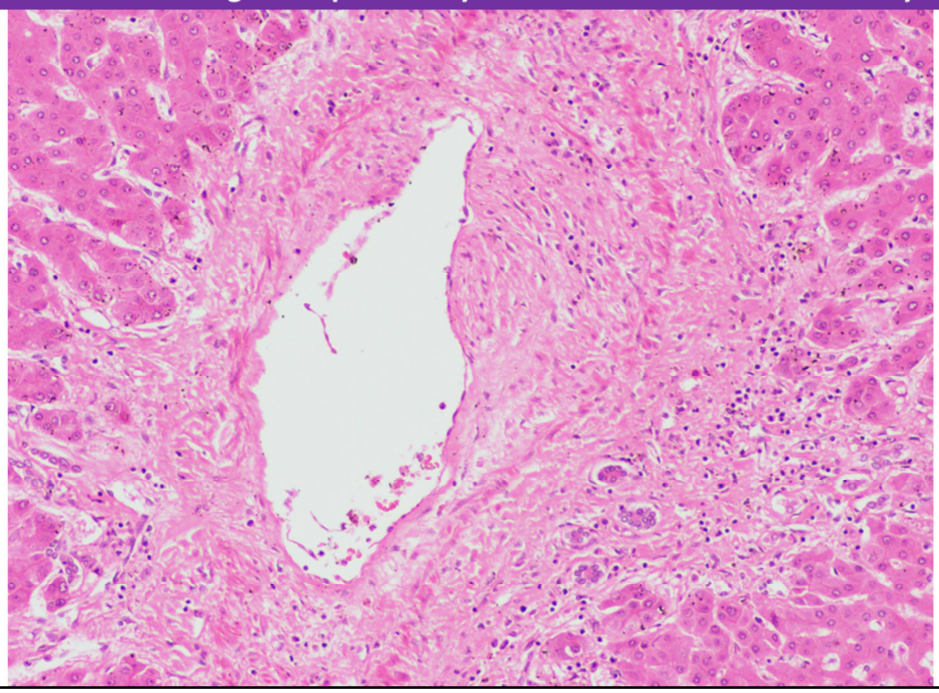
2011- Allograft hepatectomy +14y

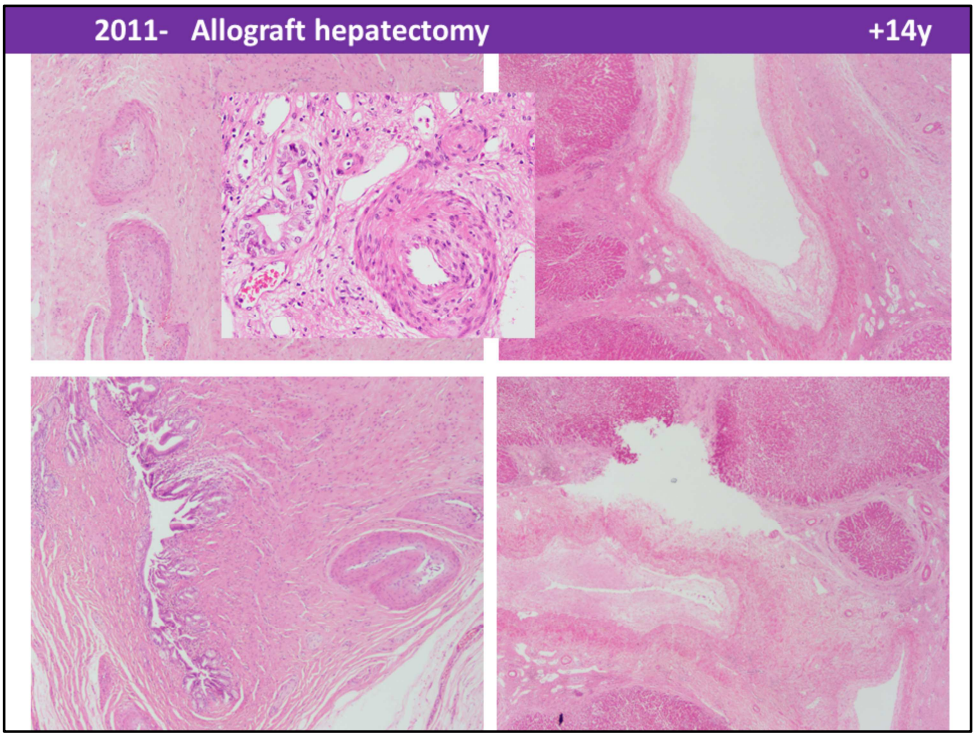


2011- Allograft hepatectomy +14y



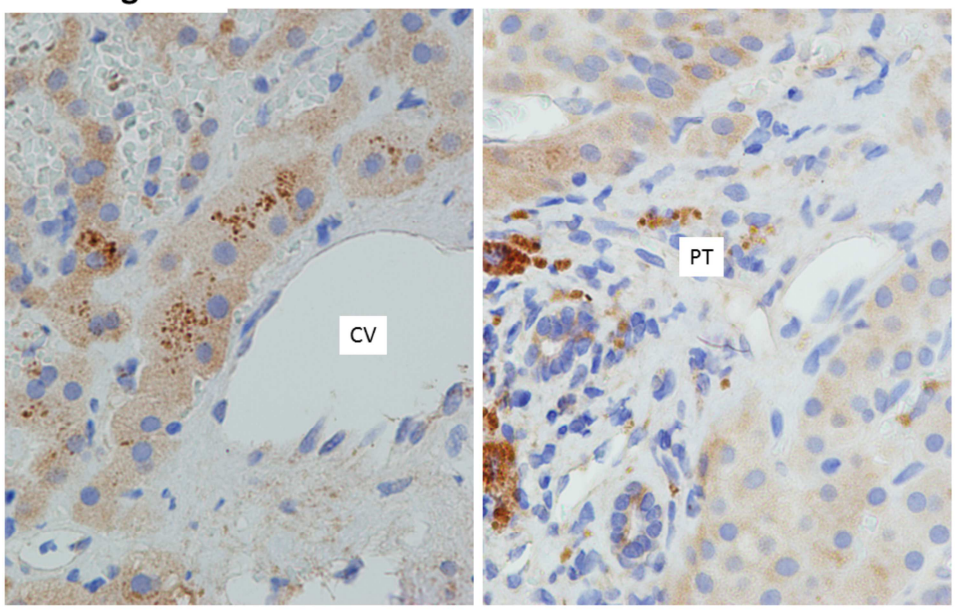
2011- Allograft hepatectomy +14y




2011- Allograft hepatectomy
+14y

2009- First Allograft +12y

C4d negative



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