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## Liver transplant pathology – messages for the non-specialist

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**Liver transplant pathology – messages for the non-specialist**

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view

Invited Review:

Liver transplant pathology – messages for the non-specialist

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There are about 650 liver transplants per year in 7 centres in the UK, with a 5 year survival rate of 75-80% (1) and about 7000 patients alive with a transplanted liver. Patients may live a distance from the transplant centre, and long term follow-up may be shared with the local hepatologist; histopathologists outside the transplant centre may therefore receive late post-transplant biopsies.

These biopsies are challenging with a wide differential diagnosis. Because of the importance of comparison with previous biopsies and of good clinic-pathological correlation, it is recommended that post-transplant biopsies are always referred to the pathologist at the transplant centre(2) However, the local pathologist often provides the initial opinion. This article focuses on these late biopsies, where the differential diagnosis broadens beyond the preservation/reperfusion changes, acute rejection and effects of surgical/post operative complications that dominate the first 3 months post-transplant.

The purpose of this article is twofold. Specifically as a guide to pathologists working outside transplant centres who may receive late post transplant liver biopsies. Also generally, to emphasize the three stage approach – (i) global pattern recognition, (ii) systematic evaluation of biopsy features, (iii) importance of clinical context – necessary in liver biopsy interpretation. In this regard, transplant biopsies are a subset of medical liver biopsies reviewed at the liver centre; understanding when and how the original clinico-pathological diagnoses are revised should enable some pitfalls to be avoided(3).

Late post transplant liver biopsies are obtained to investigate changes in liver enzymes/function tests, or as protocol biopsies particularly in hepatitis C or teenage patients. Like all medical liver biopsies, they may show a kaleidoscope of alterations including inflammation, structural changes, fibrosis, and cellular changes in hepatocytes and cholangiocytes, from which it is the task of the histopathologist, in collaboration with the hepatologist, to deduce the most appropriate clinicopathological explanation. Biopsy histology is one of an array of diagnostic tests (with biochemistry, immunology, virology and imaging) available to the hepatologist, and the histopathologist's role in the team is less often to make a single specific diagnosis, and more to guide further investigations, distinguish among potential causes of liver injury, and/or compare with previous biopsies

for the effect of intervention. A diagnosis of rejection is often made by non-specialist clinicians and pathologists, but is actually rather rarely the cause of late dysfunction unless there is a change in immunosuppression.

Liver transplantation pathology is comprehensively reviewed in standard texts(4) and review articles(5-7). There are excellent recent reviews that give detailed accounts of the different diagnostic entities underlying liver biopsy alterations (8-9). This article is more a 'where to start?' strategy for a non-specialist. The description of diagnostic patterns in liver disease by Bateman(10) in a previous Histopathology review also emphasised the three stage approach to medical liver biopsy diagnosis, in the non-transplant setting.

In general, biopsies will show some degree of inflammatory infiltrate, which may be accompanied by some fibrosis or architectural distortion and ductular reaction, and perhaps with some steatosis or cholestasis. In 2006, the Banff Working Group produced a helpful publication on the interpretation of late post transplant biopsies(11). This focuses on the differential diagnosis of inflammatory changes, based on the distribution, severity and nature of the inflammation among seven different compartments of the liver biopsy. Their tabulated summary is reproduced here with permission (table 1), and colour and shading has been added to emphasise the characteristics of the different pathologies. It is a helpful structure that (by excluding rejection from the list of differentials) can be equally applied in a non-transplant setting.

Most diseases leading to liver transplantation in adults can recur in the graft (not so in children where the majority of transplants are done for biliary atresia or inherited metabolic disease). The differential diagnosis in adult liver transplant biopsies includes rejection, recurrent disease, surgical complications (vascular and biliary) and *de novo* liver disease including autoimmune hepatitis, infection and drug reaction. As the Banff authors comment(11), 'interpretation of these biopsies can be quite difficult...'

There are caveats – more than one insult can contribute to the liver injury, and features of many overlap. In general, the more severe the inflammation, the more likely the pathologist can resolve it into one or more definite diagnoses – mild and patchy disease is

likely to be non-specific histologically, and its significance only attributable by detailed clinical correlation, or apparent in retrospect.

### Portal inflammation

Some degree of portal inflammation is usual in post transplant biopsies – determining its significance depends on the distribution, severity and composition of the inflammation and associated interface activity.

### Allograft rejection:

Histopathologists outside transplant centres may be tempted to diagnose rejection in any post transplant biopsy that shows inflammation. However in practice, rejection is a relatively rare diagnosis in late post transplant biopsies, and the diagnosis requires clinical corroboration. Other causes of portal inflammation need to be considered. In particular, hepatitis C and autoimmune hepatitis can show features that overlap closely with acute (cellular) rejection(12), and biliary disease with chronic (ductopenic) rejection (each considered further below).

In liver transplantation, most episodes of acute cellular rejection occur in the first few weeks following transplant, but it may occur at any time. The classic triad of portal tract features(13) – mixed inflammatory infiltrate including large lymphocytes and eosinophils, bile duct damage and venular endothelial inflammation (endotheliitis) are illustrated in fig 1. While this can be seen in late biopsies, the features are usually modified towards less portal vein endotheliitis, fewer lymphoblasts and eosinophils in the portal infiltrate, and more central perivenulitis (see below)(8.9.11). Of this triad, endotheliitis is the most specific feature for rejection, and its presence results in the inclusion of rejection in the differential diagnosis. The clinical context, especially a recent change in immunosuppression, is important. Histopathological evidence of rejection will prompt adjustment of immunosuppression, and consequent improvement in liver function tests gives helpful corroboration of the diagnosis.

### Autoimmune hepatitis

Histological features of recurrent or de novo autoimmune hepatitis (AIH) in the graft overlap with those of late acute rejection; autoimmune hepatitis should be suspected if plasma cells are a conspicuous component of portal and interface hepatitis (fig 2). Conversely, liver transplant patients may have liver autoantibodies without other features of AIH. Minimal diagnostic criteria for allograft AIH are interface hepatitis, a significant titre (>1 in 160) liver autoantibodies, hypergammaglobulinaemia, and exclusion of drug or virus related hepatitis and rejection(11). Conceptually, the distinction between rejection (based on immune reactions to MHC antigens) and AIH (reaction to non-MHC graft antigen) is confusing, and pragmatically clinical management of 'immune related graft injury' with enhanced immunosuppression does not necessitate a distinction to be made at the time of biopsy interpretation, although this may become apparent subsequently.

#### Viral hepatitis

Cirrhosis due to hepatitis C is now the commonest reason for liver transplant in most programmes. Unless the virus was eradicated before transplant, re-infection of the graft is universal, and circulating viral titres return to pre-transplant levels within a few days(14). This is followed usually after 3-6 weeks by histologically apparent hepatitis, and the rate of progression of fibrosis in chronic hepatitis C is accelerated compared with infection in non-transplant patients(15). However, the rate of progression is very variable, depending on the interplay of virus, host, donor and environmental factors. Older donors, donor steatosis, rejection episodes and their treatment, and severity of early hepatitis are factors associated with rapid progression to cirrhosis which is present in about 20% recipients by 5 years(8,15). Protocol biopsies are often done (e.g. annually) to detect and treat patients with rapid fibrosis. The complex clinical decisions about treating hepatitis C and managing immunosuppression are made in transplant centres, and so biopsies performed elsewhere should be sent to the centre for review.

In general, histological features of recurrent hepatitis C are similar to non-transplant livers, and can be reported in the same way, e.g. with an Ishak Histopathology Activity Index (HAI) score(16) or Metavir score (17). The task of the histopathologist is two-fold – i) are the biopsy features all attributable to hepatitis C, or is there another pathological process

present (e.g. rejection, duct obstruction)? and ii) to document the grade and stage of chronic hepatitis.

Histological features of hepatitis C in non-transplant liver biopsies include bile duct inflammation, eosinophils and endotheliitis (12), and so distinguishing an additional component of acute rejection will be difficult. Presence of portal lymphoid aggregates and diffuse lobular disarray with apoptotic hepatocytes are features of hepatitis C-associated inflammation (fig 3), in which context a mild degree of rejection-like portal tract inflammation may also be attributed to hepatitis C. The presence of disproportionate portal features of rejection, especially in the clinical context of reduced immunosuppression and not a particularly high viral titre, is an indication for clinical treatment of rejection. This is a trade off between risks to the graft of rejection versus risks of worsening hepatitis C by increasing immunosuppression.

Rapid histological progression of hepatitis C has two patterns(8,9,15). More commonly there is high viral load with maintained immune response resulting in an accelerated version of the natural history of hepatitis C. In these transplant patients, the massive initial infection of the graft, vulnerability of an older/steatotic graft, and established immune response to hepatitis C modified by immunosuppression can account for aggressive disease, foreshortening the time to developing cirrhosis. In some, this may be associated with plasma cells and interface hepatitis – histological features of autoimmune hepatitis that may be associated with raised IgG and autoantibodies(18).

The second pattern of aggressive recurrent disease is characterised by portal and sinusoidal fibrosis swollen hepatocytes and bilirubinostasis in a patient with very high viral load(19). In these patients the inadequacy of the immune response is believed to leave the liver susceptible to unopposed cytopathic effects of the virus; quasispecies are stable, due to the lack of immune-driven viral evolution(20). The histological differential diagnosis of the cholestasis and portal fibrosis is with biliary disease, and clinical context is important in resolving this.

Hepatitis B (recurrent or new) is rarely a problem in post transplant biopsies, because the infection is controlled in recipients by immunoglobulin and antiviral treatment. If this is unsuccessful, the histological patterns of viral hepatitis B are of a chronic hepatitis, which like hepatitis C can progress more rapidly than in a non-transplant patient, or rarely these days a cytopathic 'fibrosing cholestatic hepatitis' (21).

### Biliary pathology

In the transplant setting, the differential diagnosis of biliary disease is wide, and includes ductopaenic chronic rejection, anastomotic stricture, ischaemic cholangiopathy and recurrent primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC). The key to diagnosing these is recognition of the 'biliary Gestalt'(11) – a combination of ductular reaction, portal and periportal fibrosis, +/- small bile duct loss, periportal oedema, and copper-associated protein deposition in periportal hepatocytes (fig 4). Recognition of this constellation of features grows with experience, but the one concrete objective component namely granules of copper-associated protein positive on the Shikata Orcein stain is a reliable pointer that should always prompt consideration of chronic biliary pathology. Since it can be patchy (localised around portal tracts affected by or upstream from bile duct injury/ loss) it repays searching.

The role of the pathologist is to suggest the presence of a chronic biliary pathology – this prompts further investigation with imaging, and review of clinical reasons for this complication. This may be recurrence of original disease – PSC or PBC, or bile duct stricture. Bile ducts are supplied by the hepatic artery, and non-anastomotic biliary strictures form as a result of failed healing of ischaemic injury either due to hepatic artery thrombosis or late presentation of an injury originating at the time of transplantation. Grafts with prolonged ischaemic time, non-heart beating donor, split liver or live related donor grafts and paediatric transplants(22) are associated with an increased risk of late biliary complication. The histology closely mimics PSC, including variation among portal areas and therefore susceptibility to sampling error.

Ductopaenic chronic rejection, by contrast, classically results in ductopaenia without the biliary gestalt described above, although this may develop over time(23). Ductopaenic

rejection progressing to graft loss has now become rare, due to the recognition and improved management of late acute rejection, and early chronic rejection(24) (fig 4). Histologically, early ductopaenic chronic rejection is present when more than 50% tracts contain bile ducts, but these show 'senescent' changes of irregular or atrophic appearing epithelium; in this situation portal inflammation is relatively mild, but targeting residual ducts, and sparing already ductopaenic tracts (fig 4). In the late stage there is >50% ductopaenia associated with perivenular bilirubinostasis, and often zone 3 hepatocyte loss and fibrosis(23).

### Parenchymal inflammation

A key observation in parenchymal necroinflammatory activity is the distinction between diffuse lobular hepatitis, which as in non-transplant patients may be from recurrent viral hepatitis , autoimmune or drug related, from localised perivenular (zone 3) inflammation(11,25). The latter is named 'perivenulitis' and comprises sinusoidal inflammation and hepatocyte dropout localised to acinar zone 3, often accompanied by hepatic vein endotheliitis (fig 6). This is likely to be a rejection process even if there are no portal tract features of rejection (isolated central perivenulitis)(26), although alternative causes, especially autoimmune hepatitis, need to be considered. This pattern of late rejection is associated with an increased risk of progression to ductopaenic chronic rejection.

### Sinusoidal dilatation

Perivenular sinusoidal dilatation and congestion associated with liver plate atrophy has a differential diagnosis that includes venous outflow obstruction due to hepatic vein anastomotic stenosis, veno-occlusion associated with previous perivenulitis, drug-related causes particularly azathioprine(9), and vascular disturbance due to imbalance of hepatic artery and portal vein perfusion. This histological feature prompts clinical evaluation of these potential causes.

### Fatty change

Fatty change is not a feature of transplant-specific complications, but has the same differential as in the non-transplant setting. Recurrence of original disease if that were

alcoholic, non-alcoholic fatty liver disease, or hepatitis C (particularly genotype 3) is the commonest cause.

### Fibrosis

The histopathologist's assessment of the presence, pattern and degree of fibrosis is the same as in non-transplant biopsies. Fibrosis tends to be more a feature of non-rejection complications, especially recurrent disease such as hepatitis C, or the biliary pattern of fibrosis that develops in patients with biliary disease. It gives a global indication of the severity of late post-transplant liver disease, at a time when re-transplantation may be under consideration.

### Conclusion

A structured approach to biopsy evaluation and clinical discussion is essential for optimising the value of transplant biopsies, just as it is with non-transplant liver biopsies. The distribution and severity of histological features listed in table 1 forms the basis of the histological diagnosis which set in the clinical context will lead to further investigation and/or a change in patient management. As the cohort of long term liver transplant survivors grows, more histopathologists outside transplant centres will receive their biopsies. This article is intended to support them in their initial assessment. However, it remains very important also to refer the biopsy to the patient's transplant centre for review by the transplant team. This is the first message of the title. The others – systematic approach through initial pattern recognition, evaluation of individual features, integration with clinical context (and comparison with previous biopsies) are generic to all medical liver biopsies. This is necessary for ensuring the risk of the biopsy procedure is justified by its optimal diagnostic benefit(28).

Table 1. Histological features most commonly detected with various causes of late liver allograft dysfunction. (from: Banff Working Group, Histopathology 2006).

The colour coding has been added to emphasise the histological features:

red = severity/intensity; blue = distribution – patchy or diffuse; brown = inflammatory cell type; green = associated biliary features. The shaded boxes indicate the principal abnormalities of the six main differential diagnoses in post transplant biopsies showing inflammatory pathology.

Fig 1: Acute rejection. The classic triad of portal tract features of acute cellular rejection, as seen in early post transplant biopsies. The portal inflammation is polymorphous, including eosinophils and large lymphocytes ('rejection-type' infiltrate). The bile duct inflammation can include lymphocytes and/or neutrophils (long arrow). In endotheliitis, lymphocytes attach to venous endothelium and then migrate beneath it, lifting it (open arrows). Inset = hepatic vein and zone 3 hepatocytes; in late post transplant biopsies, endotheliitis is often more evident in hepatic veins than illustrated in this early biopsy.

Fig 2: Autoimmune hepatitis. Portal inflammation and interface hepatitis. The portal inflammation is lymphocytic with prominent plasma cells (inset), and associated with interface hepatitis, but the portal vein and bile duct (arrow) do not show features of rejection. De novo autoimmune hepatitis in a patient 9 years post transplant for acute seronegative hepatitis

Fig 3: Recurrent hepatitis C. Portal inflammation with lymphoid aggregate, and diffuse parenchymal necro-inflammatory activity with lobular disarray and perivenular zonal necrosis (dotted line) in a patient 10 years post transplant for hepatitis C. Confluent necrosis is very uncommon in HCV in the non-transplant setting.

Fig 4: Biliary gestalt in a patient with non-anastomotic bile duct stricture. 4a: portal features of biliary obstruction, affecting part of the portal tract circumference (right side of picture). The portal area is expanded by ductular reaction with increased small ductular profiles in

oedematous loose fibroblastic stroma, associated with scattered inflammatory cells, including neutrophils. The ductules merge with hepatocyte cords (arrow). 4b: granules of copper associated protein in peri-portal hepatocytes demonstrated by Shikata Orcein stain. This feature should always prompt consideration of biliary pathology.

Fig 5: chronic rejection. 5a: the portal inflammation is mild but targets the bile duct epithelium. 5b: bile duct with senescent changes in the epithelium (arrow); these are most readily appreciated on a PASD stain. 5c: CK7 stain is useful in identifying ductopaenic portal tracts.

Fig 6. Central perivenulitis. Clearly demarcated inflammation and drop out of perivenular hepatocytes, with very little generalised lobular inflammation, and without portal tract features of acute rejection

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Histopathological features	autoimmune hepatitis	acute rejection	chronic rejection	chronic viral hepatitis B&C	Primary biliary cirrhosis	PSC/biliary stricture1.
<b>1 distribution, severity, and composition of portal inflammation</b>	usually <i>diffuse</i> ; predominantly <i>mononuclear</i> of <i>varying intensity</i> : often prominent <i>plasma cell</i> component	usually <i>diffuse</i> : <i>variable intensity</i> : mixed 'rejection-type' infiltrate	<i>Patchy</i> : usually <i>minimal</i> or <i>mild lymphoplasmacytic</i>	<i>Patchy</i> : <i>variable intensity</i> : predominantly <i>mononuclear</i> : nodular aggregates	Noticeably <i>patchy</i> and <i>variable intensity</i> : predominantly <i>mononuclear</i> : nodular aggregates and <i>granulomas</i>	Usually <i>patchy to diffuse</i> depending on stage: <i>mild neutrophilic, eosinophilic</i> , or occasionally <i>mononuclear</i> predominant
<b>2. Presence and type of interface activity</b>	<i>Prominent</i> and defining feature is usually <i>necroinflammatory-type</i> : often <i>plasma cell-rich</i>	<i>Focally</i> present and <i>mild necroinflammatory type</i>	minimal to absent	<i>variable</i> : usually <i>not prominent</i> : <i>necroinflammatory</i> -and <i>ductular-type</i>	<i>important</i> features <i>later</i> in disease development: <i>ductular</i> and <i>necro-inflammatory-type</i> with <i>copper deposition</i>	<i>prominent</i> and defining feature: <i>ductular-type</i> with portal and periportal oedema
<b>3. Bile duct inflammation and damage</b>	<i>variable</i> : if present, involves a <i>minority</i> of bile ducts	<i>present</i> and usually involves a <i>majority</i> of bile ducts	<i>focal</i> ongoing <i>lymphocytic</i> bile duct damage: inflammation wanes with duct loss	<i>variable</i> : if present, involves a <i>minority</i> of bile ducts	<i>granulomatous</i> or <i>focally severe</i> lymphocytic <i>cholangitis</i> is diagnostic in proper setting	periductal lamellar oedema: 'fibrous <i>cholangitis</i> ': acute <i>cholangitis</i> : multiple intra-portal <i>ductal profiles</i>
<b>4. biliary epithelial senescence changes and small bile duct loss</b>	absent or involves only a minority of ducts/portal tracts, but may be focally severe	absent or involves only a minority of ducts	senescence/atrophy/ atypia involve a <i>majority</i> of remaining ducts	absent or involves only a minority of ducts	small bile duct loss associated with <i>ductular reaction</i>	small bile duct loss associated with <i>ductular reaction</i>
<b>5. perivenular mononuclear inflammation and/or hepatocyte dropout</b>	<i>variable</i> : can involve a <i>majority</i> of perivenular regions, similar to rejection; may be <i>plasma cell-rich</i>	<i>variable</i> , if defining feature should involve a <i>majority</i> of perivenular regions: may also show subendothelial inflammation of vein	usually present but <i>variable</i>	<i>variable</i> but generally <i>mild</i> : if present, involves a <i>minority</i> of perivenular regions	<i>variable</i> , but generally <i>mild</i> : if present, involves a <i>minority</i> of perivenular regions	absent
<b>6. lobular findings and necroinflammatory activity</b>	<i>variable severity</i> : rosettes may be present and/or prominent	<i>variable</i> : if present, concentrated in perivenular regions	<i>variable</i> : if present, concentrated in perivenular regions	disarray <i>variable</i> : <i>variable severity</i> : <i>necroinflammatory</i> activity	<i>mild</i> disarray: periportal <i>granulomas</i> : periportal <i>copper deposition</i> and <i>cholestasis</i> are late features	disarray unusual: <i>neutrophil</i> clusters +/- <i>cholestasis</i>
<b>7. pattern of fibrosis during progression toward cirrhosis</b>	usually macronodular: posthepatitic pattern	rare	<i>uncommon</i> , if present, usually a venocentric pattern, may evolve to <i>biliary pattern</i> over time	usually macronodular, hepatic pattern: may be micronodular	<i>biliary pattern</i>	<i>biliary pattern</i>

Table 1.

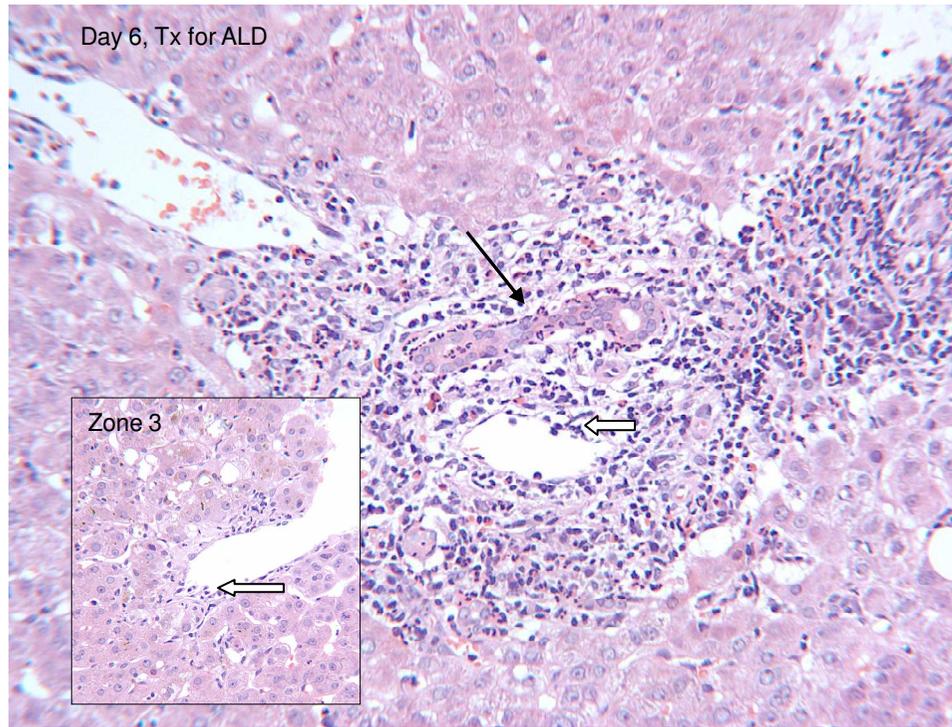


Figure 1

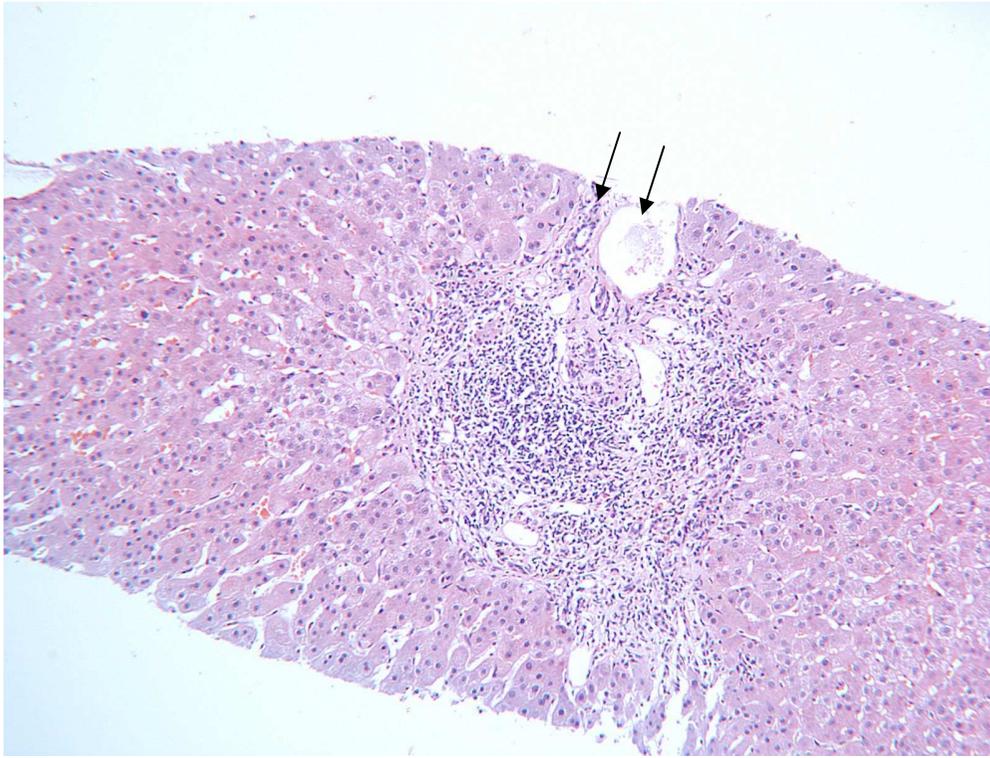


Figure 2

Review

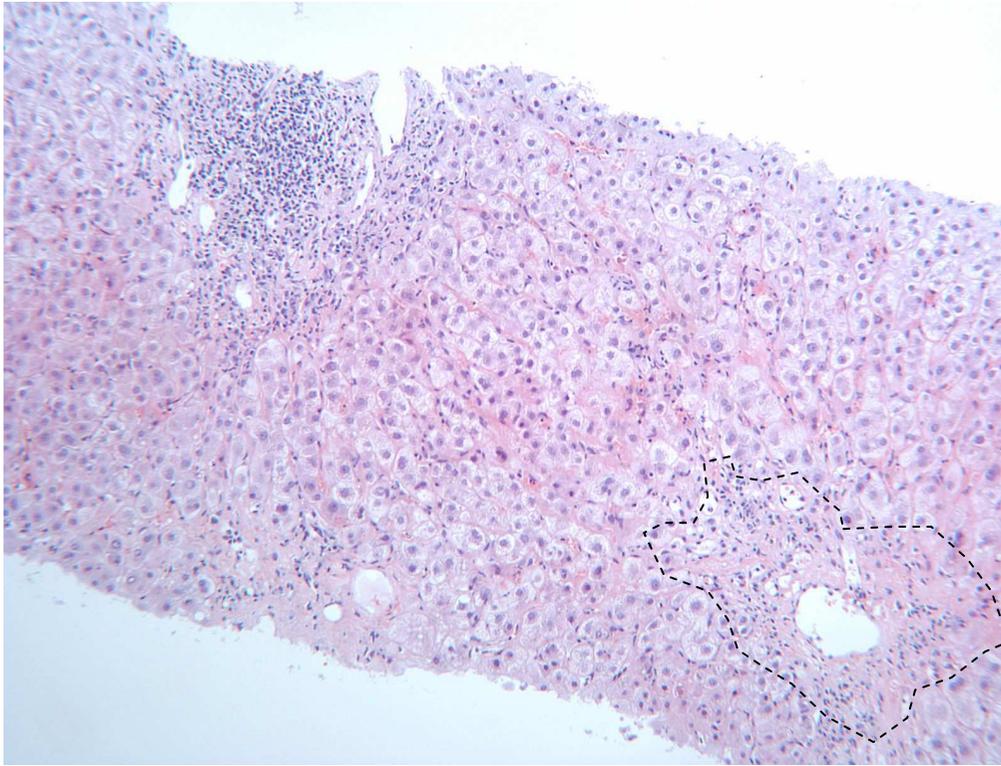


Figure 3.

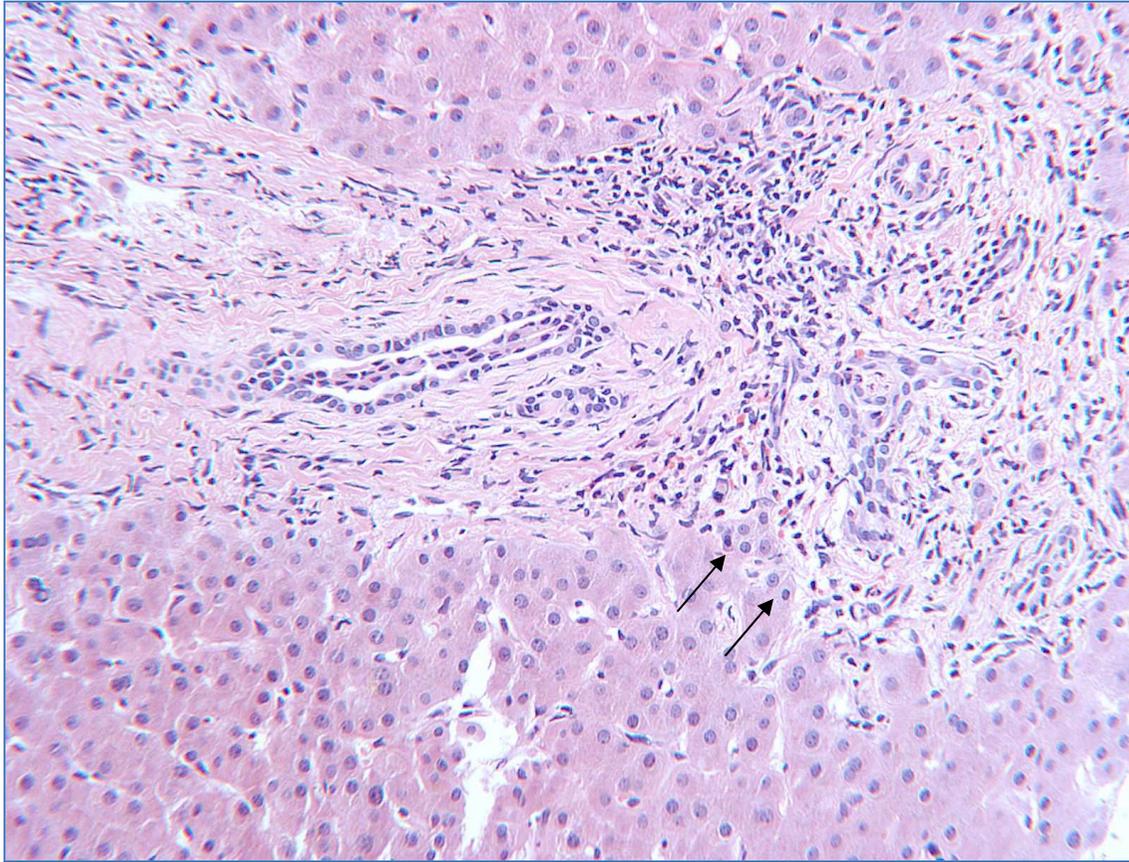


Fig 4a

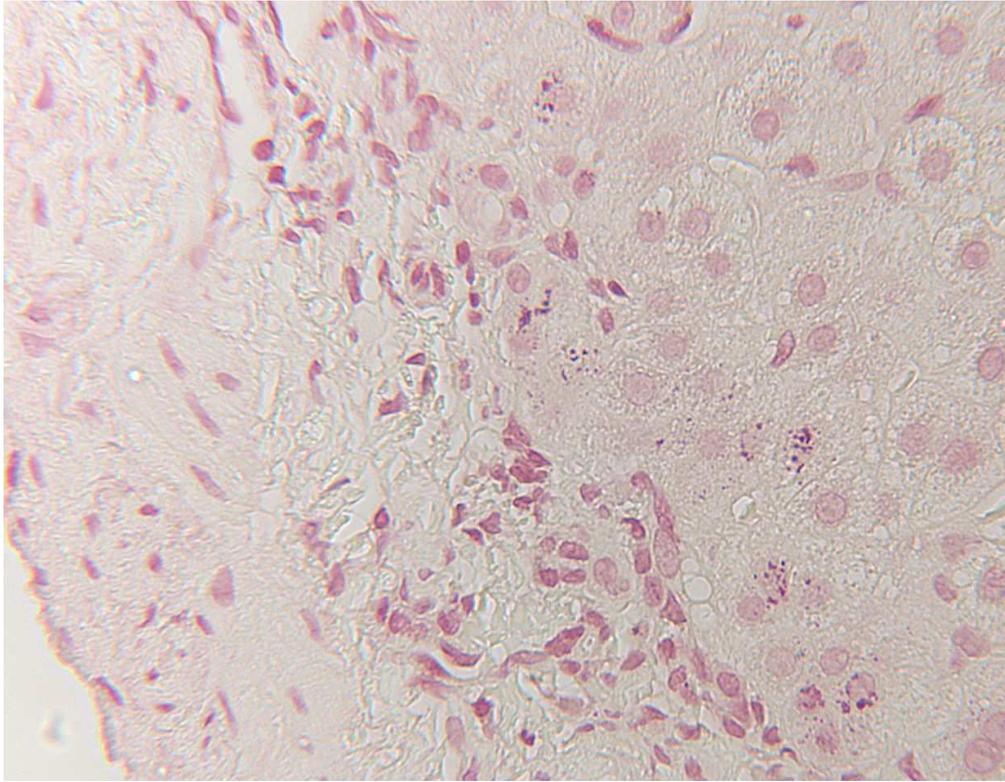


Fig 4b

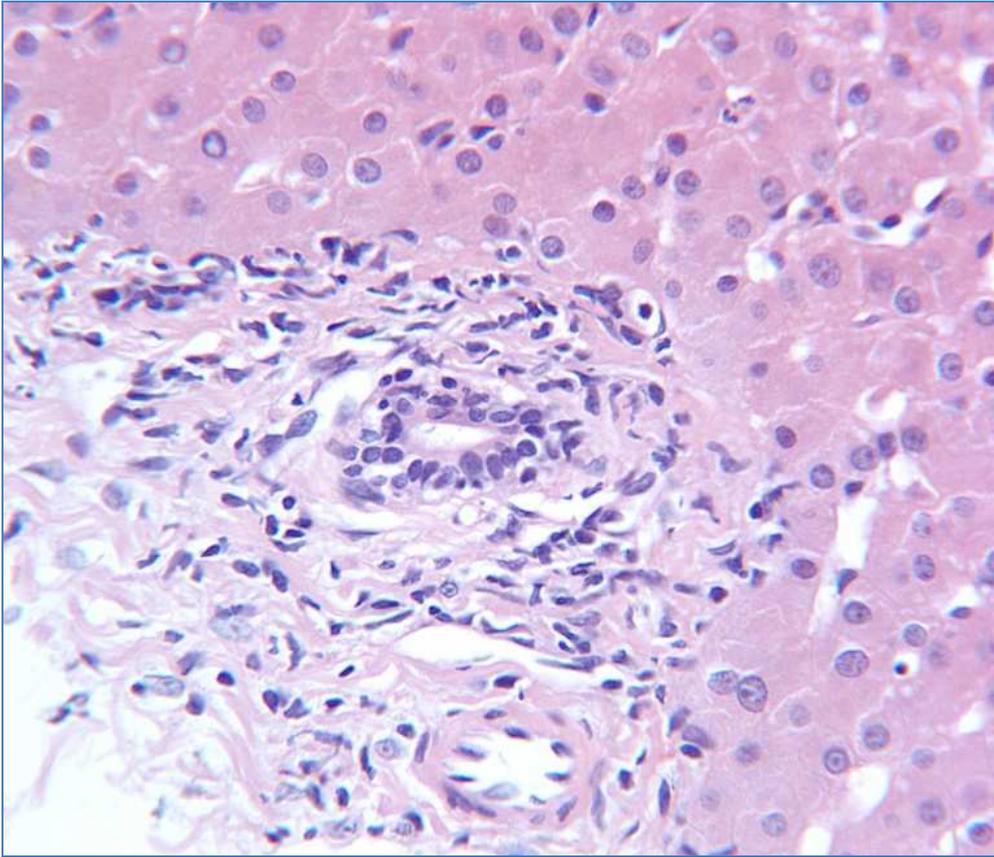


Figure 5a

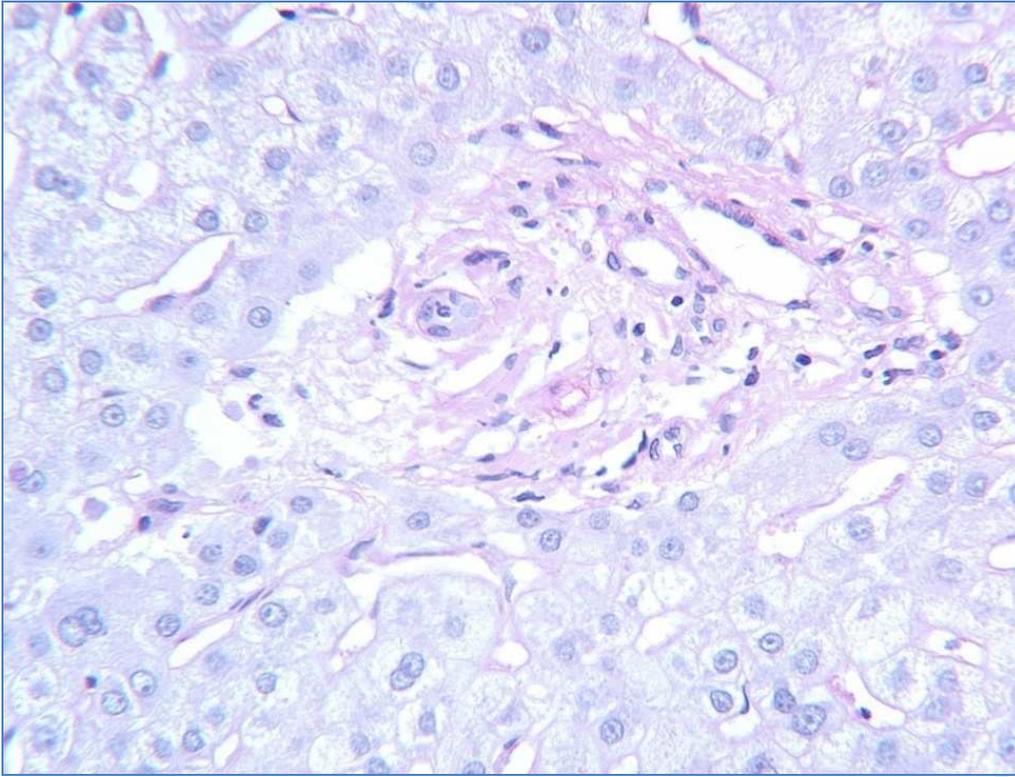


Fig 5b

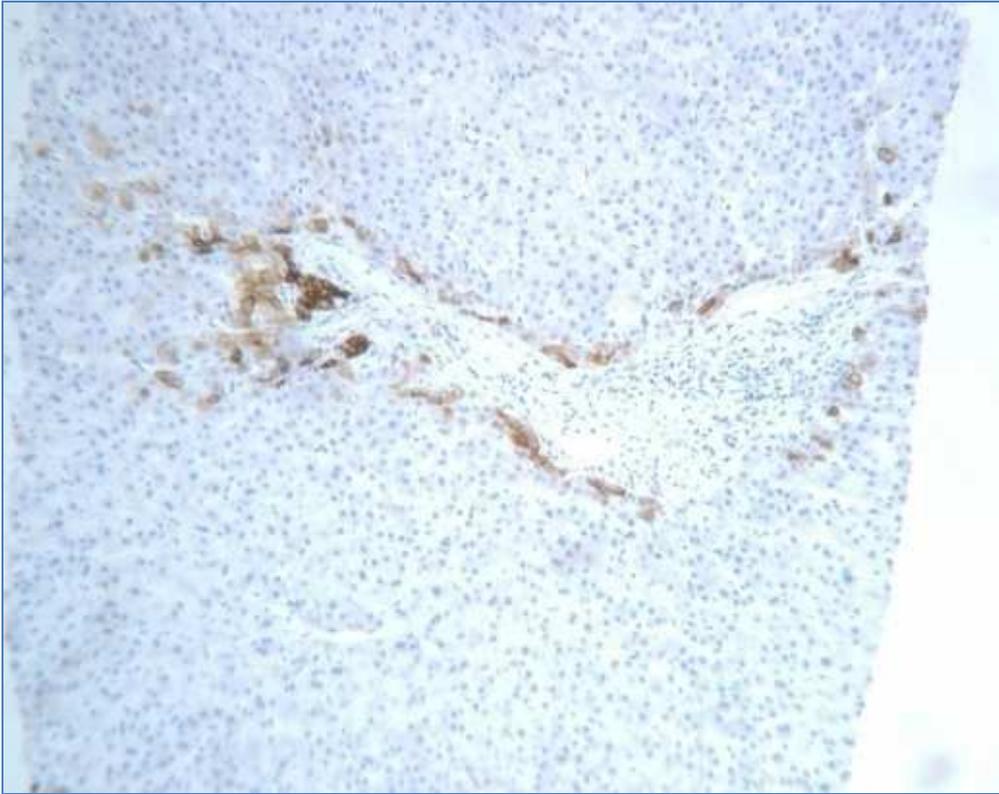


Fig 5c

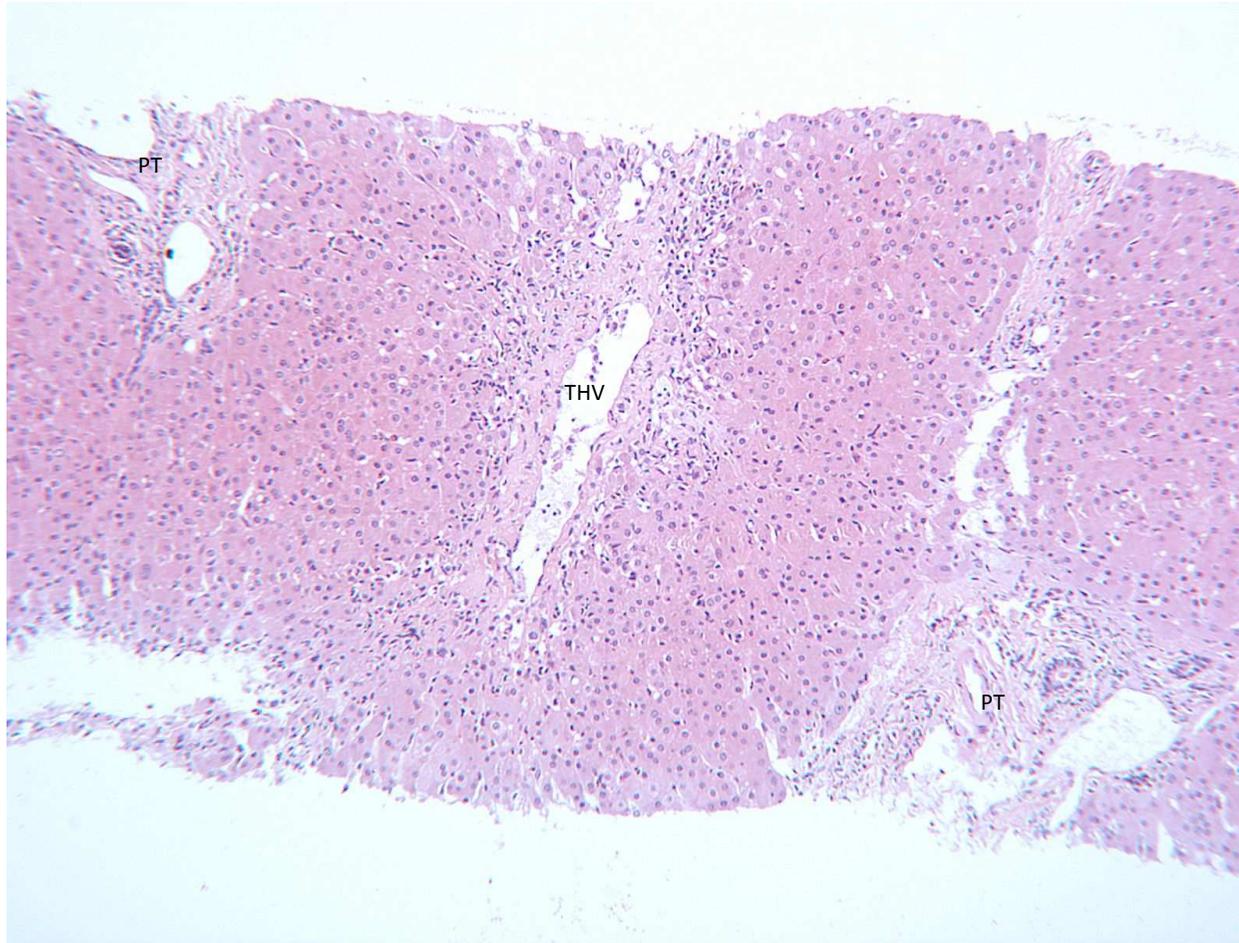


Fig 6.