Histological findings of autoimmune hepatitis

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Chapter 4.Histological findings of autoimmune hepatitis

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Abstract

Histology of autoimmune hepatitis (AIH), chronic active hepatitis, is characterized by portal inflammation with interface hepatitis. Although the basic histology of AIH is similar to that of virus-related chronic hepatitis, hepatitic changes are usually prominent in AIH compared with chronic viral hepatitis. Clinicopathological diagnosis of AIH requires exclusion of other causes of liver disease, including hepatitis virus, alcohol, drugs, metabolic disorders, and other autoimmune diseases. At present, some criteria systems considering clinicopathological findings are proposed to categorize patients as having either “definite” or “probably/atypical” AIH. Among the pathological items of a simplified AIH scoring system of the International AIH Group, in addition to evident chronic hepatitis with interface hepatitis and hepatic rosette formation, emperipolesis, indicating the close immunological interaction of lymphocytes and hepatocytes, is noted but is sometimes difficult to evaluate. In addition to classical AIH, showing chronic active hepatitis, some AIH patients show a clinically acute hepatitis-like clinical course. These patients have mostly acute exacerbation from chronic active AIH, but acute-onset AIH cases, which histologically exhibit diffuse lobular hepatitis and/or confluent necrosis including perivenular zonal necrosis (zone 3 necrosis, centrizonal necrosis), are also encountered.

4.1 Introduction

Chronic hepatitis is defined as an inflammatory disease of the liver that lasts for more than six months. Histologically, chronic active hepatitis accompanies interface hepatitis (formerly termed piecemeal necrosis). As an etiology, viral hepatitis (hepatitis B virus, hepatitis C virus, etc.), metabolic disease [nonalcoholic fatty liver disease (NAFLD), Wilson's disease, etc.], toxic agents and drugs (alcoholic liver disease, aminodarone, etc.), autoimmune disease [autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), and sarcoidosis] have been described. In particular, AIH preferably affects middle-aged women and is characterized by chronic active hepatitis related to autoimmune-mediated and continuous hepatocellular damage. Usually, it can be readily distinguished from the other two major autoimmune liver diseases, PBC and PSC, but overlap syndromes exist. However, AIH lacks pathognomonic features and histological manifestations are observed in acute and chronic liver diseases of diverse causes.

4.2 Basic histology of AIH

Basic histology of AIH includes chronic active hepatitis characterized by portal inflammation with interface hepatitis; lymphoplasmacytic infiltration and follicle-like aggregation of lymphocytes in portal tracts (Figs 1 and 2), fibrous enlargement of portal tracts with fibrous septa formation, hepatocellular damage and necrosis/apoptosis around portal tracts with the destruction of limiting plates (interface hepatitis) (Fig. 2), parenchymal necroinflammatory changes including focal necrosis (lobular hepatitis) (Fig. 3), and sinusoidal lymphocytic infiltration. In particular, interface hepatitis is a pathogenic hallmark of chronic active AIH and is prominent during disease flares. These histologies are similar to those observed in chronic active hepatitis caused by viral infection and are not specific for AIH. Interface hepatitis may occur even in biliary diseases such as PBC. However, compared with those observed in chronic viral hepatitis, the hepatitic changes that are prominent in typical AIH include the following: infiltration and accumulation of marked plasma cells in portal tracts, confluent necrosis (bridging and zonal necrosis) (Fig. 4), ballooning degeneration of hepatocytes (Fig.5) and many acidophilic bodies (apoptosis of hepatocytes) (Fig. 6), rosette formation of hepatocytes (Fig. 7), and pigmented macrophages (pigment-laden or ceroid-laden

macrophages) (Fig. 8). As for the predominant plasma cell infiltration, this feature does not occur in all patients with AIH [1]. Its presence supports the diagnosis of AIH because it is a finding that is more common in AIH (66%) than in chronic hepatitis B (40%) or chronic hepatitis C (21%). In severe cases and acute exacerbation of AIH, giant cell formation of hepatocytes (giant syncytial multinucleated hepatocytes) (Fig. 9), broad hepatocellular collapse (Fig. 10), and multiple confluent necrosis consisting zonal and bridging necrosis are observed. Cases of fulminant hepatitis, histologically showing submassive and massive necrosis, are also present. In addition to severe lobular necrosis including massive hepatocyte necrosis and drop out, regeneration of hepatocytes may be present and mimic parenchymal nodules of established cirrhosis in the recovery phase of fulminant AIH.

4.3 Pathogenesis of AIH from the aspect of pathogenic and regulatory helper T cells

Several studies, including animal model studies, have been reported for the pathogenesis of AIH. It is postulated that an environmental agent, either a drug, virus, or other agent, appears to trigger a T cell-mediated cascade directed against hepatocellular antigens in genetically predisposed individuals to cause AIH. Immunohistochemically $CD8^+$ T cells are a dominant subset of lymphocytes observed within the area of interface hepatitis and $CD4^+$ T cells predominate within the portal tracts [2]. $CD4^+$ helper T cells are essential regulators of immune responses and inflammatory diseases. Immunoreactivity to intra- and extracellular antigens is regulated mainly by two different types of memory $CD4^+$helper T cells, i.e., Th1 and Th2 cells, which are principally distinguished by their production of different cytokines and their ability to induce either cellular (Th1) or humoral (Th2) immune reactions. The advancement of the understanding of polarized Th1 and Th2 cells in human diseases suggests that the balance between these two subsets is altered in autoimmune disorders; organ-specific autoimmune diseases, including AIH, are mainly mediated by Th1 cells, whereas the Th2 subset predominates in systemic autoimmune disorders [3-5]. Immunohistochemically, Th1 and Th2 cells are easily distinguishable by the transcription factors T-box expressed in T cells (T-bet) and GATA-binding protein-3 (GATA-3), respectively, in addition to Th1-type cytokines (IL-2 and IFN-γ) and Th2-type cytokines (IL4, IL10, and IL13). In fact, many T-bet-positive lymphocytes

infiltrate the portal tracts and parenchyma (Fig. 11), whereas GATA-3-positive cells are scarce. Of late, a third pathogenic type, Th17 cells, and their association with the chronic inflammation present in autoimmune diseases via the production of the proinflammatory cytokines IL-17, IL-22, and TNF-α, have been noted [6-9]. Th17 cells are elevated in the circulation and liver of patients with AIH and contribute to autoimmunity against hepatocytes by inducing the secretion of IL-6 by these cells [10]. Both natural Tregs (nTregs, $Foxp3^{+}CD25^{+}$Tregs), which originate in $CD4^{+}$ T cells in the thymus, and induced Tregs (iTregs, $Foxp3^{+}$Tregs), which develop in the periphery, can play a role of dominant immunosuppression on effector T cells and antigen-presenting cells. Patients with AIH have a reduced number and function of $CD4^{+}CD25^{+}FOXP3^{+}$Tregs [11,12]. However, a controversial study has reported that the frequency and function of circulating Tregs is not impaired in AIH (Fig. 11) [13].

4.4 Pathological diagnosis—histological components of the AIH diagnostic scoring system

The clinicopathological diagnosis of AIH requires the exclusion of other causes of liver disease, including viral hepatitis, alcohol and drug abuse, metabolic disorders (NAFLD and NASH), and other autoimmune diseases. In particular, the pathological differentiation of AIH from chronic viral hepatitis and the presence of AIH superimposed on HCV-infected patients is difficult or impossible in most cases. Pathologically, the histological difference between AIH and chronic viral hepatitis depends on the relative evaluation of several findings regarding chronic active hepatitis. Therefore, some systems of criteria that take into consideration clinicopathological findings have been proposed to categorize patients as having either “definite” or “probably/atypical” AIH. The criteria of the Intractable Hepatobiliary Disease Study Group in Japan (2013) [14] includes the following: 1) exclusion of other causes of liver disease, 2) positivity for the antinuclear antibody (ANA) and/or antismooth muscle antibody, 3) increased IgG level (>1.10 times the upper normal limit), 4) interface hepatitis and plasma cell infiltration in liver tissues, and 5) marked efficacy of steroid therapy. Typical AIH is defined as the presence of 1) and another three items among 2)–5), and the atypical cases are defined as those exhibiting 1) and another one or two item(s) among 2)–5). In addition to these Japanese AIH criteria, the AIH scoring system

of the International AIH Group (IAIHG) is useful. At present, modified criteria (1999) [15] and simplified criteria (2008) [16] are used. The former consist of many items and are complex; however, it is possible to adequately distinguish AIH from other liver diseases, particularly primary biliary diseases, such as PBC and PSC, and chronic viral hepatitis. Pathological items consist of interface hepatitis (+3), predominantly lymphoplasmacytic infiltrate (+1), rosette of liver cells (+1), none of the above (−5), biliary changes (−3), and other changes (−3), which make up score 5 in full score 29. The most important point is that biliary changes and other changes suggestive of other hepatobiliary diseases, including PBC and PSC, and a different etiology, respectively, provide negative points toward the accurate identification of AIH alone. “Biliary changes” refers to bile duct changes that are typical of PBC or PSC (i.e., granulomatous cholangitis or severe concentric periductal fibrosis with ductopenia established in an adequate biopsy specimen) and/or a substantial periportal ductular reaction with copper/copper-associated protein accumulation (Fig. 12). The deposition of copper reflects chronic cholestasis [17,18], and orcein staining is very useful to detect the deposition of copper-binding proteins. This deposition in the early stage of chronic liver diseases suggests cholestatic liver diseases, such as PBC, PSC, and Wilson’s disease; however, in advanced liver diseases, including cirrhosis, this deposition in hepatocytes is usually observed, regardless of etiology. Pathologists, therefore, have to evaluate orcein staining results with caution to avoid over diagnosing biliary diseases. In contrast, the simplified criteria [16] have been proposed for the rapid diagnosis and treatment for AIH and are useful to nonspecialized and specialized hepatologists. Regarding the pathological items in this criteria, three categories are defined for grading histology and give out a score of 0–2 in full score 8; atypical histology (0 points), histology compatible with AIH (1 point), and typical histology (2 points). In addition to evident hepatitis as a necessary condition, interface hepatitis, lymphocytic/lymphoplasmacytic infiltrates in portal tracts and extends into the lobule, emperipolesis, and hepatic rosette formation are regarded as typical for the diagnosis of AIH. To be considered typical, each of the three features of typical AIH histology has to be present. Compatible features are a picture of chronic hepatitis with lymphocytic infiltration without all the features that are considered typical. Histology is considered atypical when signs of another diagnosis, such as steatohepatitis, are present. These findings reflect chronic

hepatitis with severe activities; however, it is impossible to establish a definite diagnosis of AIH on the basis of these findings because they are not specific to AIH. Because atypical AIH cases, such as acute onset and excavation AIH, are probably ruled out as being non-AIH when using the simplified criteria, the modified criteria (1999) should be applied in these cases. Moreover, steatohepatitis is considered as a disease that is difficult to differentiate from AIH based on these criteria, and ANA is detected in approximately one third of cases of NASH and NAFLD [19,20], although pathological differentiation is relatively easy on liver biopsy.

Among the histological findings of the simplified IAIHG criteria, emperipolesis is unfamiliar in the hepatology field but is pathologically well known as a characteristic of the Rosai–Dorfman disease (sinus histiocytosis with massive lymphadenopathy). Emperipolesis is an active penetration by one cell into and through a larger cell and is immunologically the strongest pattern of cell-to-cell contact (Fig. 13). Although lymphocytes are frequently found in close contact with hepatocytes and bile ducts in various hepatobiliary diseases, the presence of emperipolesis indicates the close immunological interaction of immune competent cells (lymphocytes) and target cells (hepatocytes) in AIH. In addition to rosette formation of hepatocytes, this emperipolesis is frequently observed in hepatocytes around the interface hepatitis of AIH with severe hepatitic changes (Fig. 14). At present, emperipolesis is noted as a pathological finding and is included in the simplified criteria of AIH. However, this finding was primarily reported in the field of hepatology as a histological finding of HBV-related chronic viral hepatitis [21] and is found in other hepatitic diseases with chronic active hepatitis and AIH. In practice, in the establishment of a pathological diagnosis using HE staining, it is always difficult to distinguish emperipolesis from apoptotic body-laden macrophages and to differentiate whether lymphocytes are located inside or outside of hepatocytes. Because the presence or absence of emperipolesis greatly affects the score of simplified AIH criteria (1 in a full score of 8) [16], the survey of emperipolesis is a heavy burden for pathologists.

Compared with the histology of chronic viral hepatitis, several of the findings that indicate the possibility of AIH described above are observed in AIH, but all these findings are not observed in needle liver specimens. However, the presence of highly active hepatitis is necessary for the pathological diagnosis of pretreated AIH cases, and

chronic hepatitis with broad hepatocellular necrosis should be suspected as AIH. Bile duct damages are thought to be a histological characteristic of PBC and PSC. However, bile duct damage is often observed in AIH with severe portal inflammation (Fig. 15). This bile duct damage is called hepatitic bile duct damage or hepatitis-associated bile duct damage and is often observed in chronic active hepatitis, including AIH and chronic viral hepatitis (in particular, HCV-related disease) (Fig. 15). These bile duct damages sometimes accompany destructive changes (up to 12% of biopsies) [1], and resemble chronic nonsuppurative destruction cholangitis (CNSDC) of PBC (Fig. 15). The observation of bile duct lesions alone cannot be used to differentiate AIH from PBC [22]. However, the bile duct loss found in biliary diseases such as PBC and PSC is rarely observed in AIH.

4.5 Histological staging and grading system

Liver biopsy provides information regarding the staging of fibrosis and the degree of hepatic inflammation as well as the diagnosis of AIH. However, there is no scoring system that reflects the unique histological features of AIH. Regarding the staging and grading systems for AIH, four systems, such as those described by Batts and Ludwig [23] and Scheuer (Table 1) [24], the French Metavir system [25], and the modified histological activity index (Table 2) [26] for chronic viral hepatitis are diverted. In Japan, the New Inuyama Classification [27] is diverted as a grading and staging system that reflects activity and fibrosis, although this originally should be applied to chronic viral hepatitis. In this classification, the degree of necroinflammatory change (grading or activity system) is classified into the following four categories that take into consideration portal inflammation including interface hepatitis and parenchymal inflammation: A0 (minimal: no or minimal necroinflammatory change), A1 (mild: mild necroinflammatory change), A2 (moderate: moderate necroinflammatory change), and A3 (severe: marked necroinflammatory change including confluent necrosis, such as zonal and bridging necrosis). A staging score has been developed to reflect the extent of portal fibrosis. Fibrosis stages are as follows: F0 (no fibrosis: no or minimal portal fibrosis), F1 (mild fibrosis: as above, with portal fibrous enlargement), F2 (moderate fibrosis: as above, with bridging fibrosis), F3 (severe fibrosis: as above, with lobular disarray), and F4 (cirrhosis).

4.6 Liver cirrhosis

Cirrhosis is the terminal stage of AIH. However, at the diagnosis of AIH, 6.4% of AIH cases in Japan have already progressed to cirrhosis [28]. Moreover, cirrhosis of AIH is a risk factor for hepatocellular carcinoma, although its incidence is lower than that observed in hepatitis virus-related cirrhosis [29]. In general, cirrhosis is thought to be an irreversible terminal stage, regardless of etiology. However, in cases that exhibit great clinical improvement after immunosuppressive treatment, fibrosis and cirrhosis regression, as well as hepatocellular regeneration, result in the disappearance of the remnant of cirrhosis. In contrast, AIH-related cirrhosis, although inactive, is thought to be caused by a burnt-out process without specific laboratory findings and absent disease activity. Therefore, as in the preceding diseases of cryptogenic cirrhosis, AIH and nonalcoholic steatohepatitis are usually at the top of the list.

4.7 Variations of AIH

4.7.1 Acute AIH

Some AIH patients show a clinically acute hepatitis-like clinical course. These AIH patients have mostly acute exacerbation from chronic active AIH (Fig. 16) but acute-onset or fulminant AIH cases with diffuse and severe hepatocellular damage without definite chronicity, such as fibrosis and preceding liver dysfunction, have also been reported (Figs 17 and 18) [30]. These acute AIH cases have higher serum bilirubin, transaminase, and γ-GTP compared with ordinary chronic AIH. In contrast, the serum levels of IgG and γ-globulin and the titer of autoantibodies are not generally high. Therefore, it is difficult to diagnose acute AIH using the international criteria as mentioned above. Liver biopsy is useful for the diagnosis of acute AIH. There is portal inflammation and diffuse lobular necroinflammation (Fig. 17). Perivenular zonal necrosis and bridging necrosis among portal tracts and central veins, and rarely periportal zonal necrosis, may accompany lobular disarray (Figs 18 and 19) [31-33]. In some cases, zonal necrosis (zone 3 necrosis, centrozonal necrosis) located around the central vein, similar to a characteristic of drug-induced liver injury, is prominent (Fig.20) [34,35]. Zone 3 necrosis has not been formally included in the histological features of AIH but is thought to be a characteristic feature of acute-onset AIH.

4.7.2 PBC–AIH overlap syndrome

AIH and PBC may simultaneously or metachronously coexist in some patients, which is designated as PBC–AIH overlap syndrome. Previous studies suggest that combination therapy of ursodeoxycholic acid (UDCA) and corticosteroids may be effective in these cases. Although its pathogenesis has been discussed for a long time, according to the statements of IAIHG, this overlap syndrome has been regarded as a subtype of PBC with the feature of AIH-like severe hepatitic change [36] and corresponds to the disease group that has been formerly called hepatitic PBC. Although AIH-like features are dominant in liver histology, distinct PBC features, such as CNSDC and bile duct loss, are also observed (Fig.21).

Chazouilleres's criteria [37] (Paris criteria) has been used as the diagnostic criteria for this overlap syndrome, and the simplified AIH system of the IAIHG has been used as the criteria for the AIH feature in PBC. Steroid therapy (PSL) is recommended in addition to UDCA for cases that are considered to be PBC–AIH overlap syndrome. The Intractable Hepatobiliary Disease Study Group in Japan (2011) recommends PSL in addition to UDCA for cases that are considered to be PBC–AIH overlap syndrome and simultaneously meet the two following criteria: (1) diagnosis of PBC using the criteria of the Intractable Hepatobiliary Disease Study Group in Japan (2010) and (2) diagnosis of probable/definite AIH using IAIHG simplified criteria (2008). Regarding liver histology, hepatitic activity (HA) scores in the PBC grading/staging system should be used as follows: 0 points for HA score 0 or 1, 1 point for HA score 2, and 2 points for HA score 3 [38,18,39]. Because the presence of emperipolesis, which is not familiar to clinicians and even pathologists, is not required to survey the disease, pathological evaluation becomes relative easy.

4.8 Conclusion

In the diagnosis and management of AIH, liver biopsy is an essential element, because individual histological, serological, and clinical features are not specific for the diagnosis of AIH. Histological examination of liver biopsies helps exclude other potential causes of liver disease and identify variant syndromes. Therefore, AIH is thought to be a clinicopathological entity, and the communication between pathologists

and clinicians is crucial in AIH.

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Figure legends

Fig.1 Typical autoimmune hepatitis (AIH) showing chronic active hepatitis. Enlargement of portal tracts and bridging formation (A, arrow) are observed. In inflamed portal tracts, bile duct damage is observed (B, arrow).

Fig.2 Typical autoimmune hepatitis (AIH) showing chronic active hepatitis. In enlarged portal tracts, severe inflammatory cells infiltration and follicle-like aggregation (*) are observed (A). Interface hepatitis is also prominent (arrows in A and B). Inflammatory cells consist of lymphocytes and plasma cells (B). B is a higher magnification of A.

Fig.3 Parenchymal change in autoimmune hepatitis (AIH) showing chronic active hepatitis. In parenchyma, many focal necrosis are observed. This lobular hepatitis is prominent in AIH.

Fig.4 Confluent necrosis. Bridging necrosis (A, arrow) and perivenular zonal necrosis (B) are observed in AIH cases.

Fig.5 Ballooning degeneration of hepatocytes (*) is observed in the periportal area in autoimmune hepatitis (AIH).

Fig.6 The present of acidophilic bodies indicating the apoptosis of hepatocytes (arrows) reflects the marked parenchymal hepatitis in autoimmune hepatitis (AIH).

Fig.7 Hepatocyte rosette formation (arrow) around a severe interface hepatitis area.

Fig.8 Pigmented macrophages (arrows) are scattered in a necrotic area of autoimmune hepatitis (AIH).

Fig.9 Giant syncytial multinucleated hepatocytes (arrows) are present in some

autoimmune hepatitis (AIH) cases.

Fig.10 Broad collapse of hepatocytes (arrows) in acute exacerbation of autoimmune hepatitis (AIH).

Fig.11 Immunohistochemistry for T-bet (A) and Foxp3 (B). Many T-bet-positive Th1-type T cells are observed in portal tracts (PT) and parenchyma (P) (A). Foxp3-positive Treg cells are scattered in PTs (B).

Fig.12 Biliary changes raised by modified criteria (1999) of the autoimmune hepatitis (AIH) scoring system. A: Granulomatous cholangitis in primary biliary cirrhosis. B: Severe concentric periductal fibrosis in primary sclerosing cholangitis. C: Ductopenia. The portal vein (P) and artery (A) are found, but the bile duct is missing. D: Orcein staining. Copper-binding proteins are scattered in hepatocytes.

Fig.13 Immunological contact pattern between target cells and lymphocytes. Emperipolesis is a unique feature of penetration of lymphocytes into hepatocytes, and the tightest pattern of target cells (hepatocytes) and effector cells (lymphocytes).

Fig.14 Emperipolesis in autoimmune hepatitis (AIH). Emperipolesis is observed around the interface area. Although arrows indicate emperipolesis, all arrows are possibly hard to evaluate as emperipolesis.

Fig.15 Bile duct damage (hepatitic bile duct injury) in autoimmune hepatitis (AIH). Arrows denote the damaged interlobular bile ducts at various degrees. In particular, bile ducts in C and D show destructive changes resembling chronic nonsuppurative destructive cholangitis (CNSDC) of primary biliary cirrhosis (PBC).

Fig.16 Acute exacerbation of autoimmune hepatitis (AIH). A: Many focal necroses are

diffusely seen in parenchyma. B: Bridging necrosis (arrow) is observed between enlarged portal tracts with inflammation (P).

Fig.17 Acute-onset autoimmune hepatitis (AIH) case. In parenchyma, many focal necroses and pigmented macrophages are scattered and accumulate around the central vein (C). Portal tracts (P) are almost preserved.

Fig.18 Acute-onset autoimmune hepatitis (AIH) case without preceding liver dysfunction. A: Lower magnification. A diffuse inflammatory change is observed. B: Perivenular zonal necrosis is observed (arrows). C: Bridging necrosis is seen between portal tracts. D: Although mild inflammation and edema are observed in portal tracts, reticulin staining shows no distinct fibrous enlargement.

Fig.19 Acute-onset autoimmune hepatitis (AIH) case without preceding liver dysfunction and drug intake. Antinuclear antibody is positive (1280×). In addition to diffuse lobular hepatitis, periportal zonal necrosis is observed (arrows, A). Azan–Mallory staining indicates and absence of fibrosis in the zonal area (arrows, B).

Fig.20 Two cases of acute-onset autoimmune hepatitis (AIH) showing zone 3 necrosis. A and B: Perivenular zonal necrosis with hemorrhage is observed but portal inflammation is minimal (P). C and D: Perivenular zonal necrosis resembling hepatocellular necrosis of drug-induce liver injury is observed.

Fig.21 Two cases of primary biliary cirrhosis–autoimmune hepatitis (PBC–AIH) overlap syndrome (hepatitic PBC). In addition to chronic nonsuppurative destruction cholangitis (CNSDC) (arrows), marked portal inflammation is observed. In the case on the right (B), interface hepatitis and lobular hepatitis (*) are also prominent.

Scheuer classification for grading and staging of chronic hepatitis

Grade	Portal/periportal activity	Lobular activity
0	None	None
1	Portal inflammation	Inflammation but no necrosis
2	Mild piecemeal necrosis	Focal necrosis or acidophil bodies
3	Moderate piecemeal necrosis	Severe focal cell damage
4	Severe piecemeal necrosis	Damage includes bridging necrosis

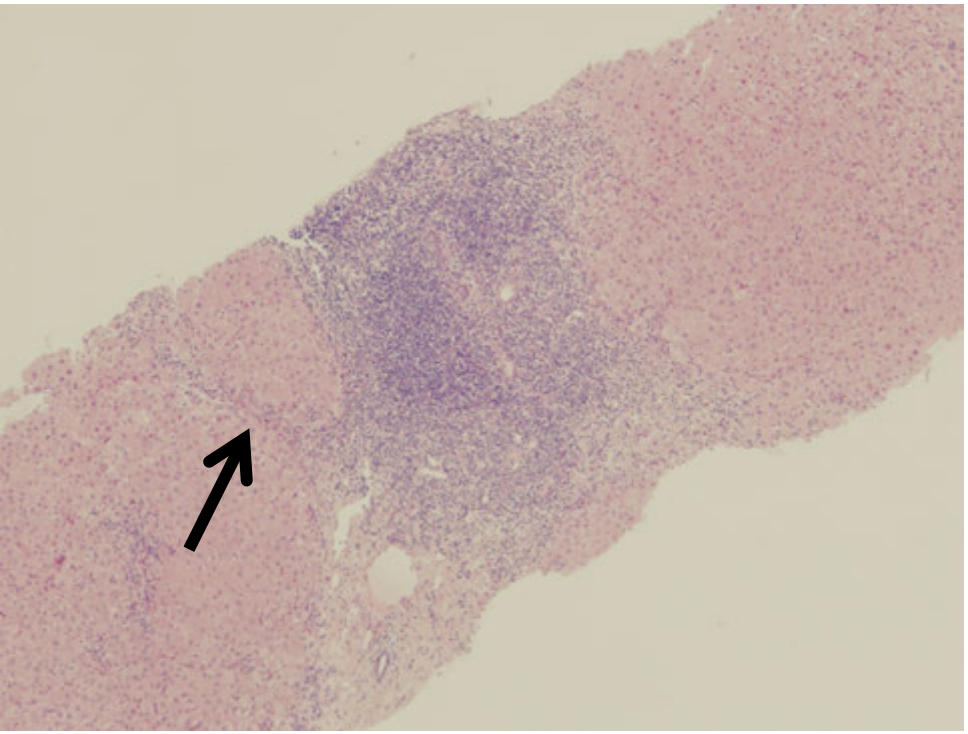
Stage	Fibrosis
0	None
1	Enlarged, fibrotic portal tracts
2	Periportal or portal-portal septa, but intact architecture
3	Fibrosis with architectural distortion, but no obvious cirrhosis
4	Probable or definite cirrhosis

Table 1

Ishak modified hepatic activity index (HAI) for scoring of necroinflammatory activity and staging in chronic hepatitis

Necroinflammatory scores	
(A) Periportal or periseptal interface hepatitis (piecemeal necrosis)	
Absent	0
Mild (focal, few portal areas)	1
Mild/moderate (focal, most portal areas)	2
Moderate (continuous around <50% of tracts or septa)	3
Severe (continuous around >50% of tracts or septa)	4
(B) Confluent necrosis	
Absent	0
Focal confluent necrosis	1
Zone 3 necrosis in some areas	2
Zone 3 necrosis in most areas	3
Zone 3 necrosis+occasional portal-central (P-C) bridging	4
Zone 3 necrosis + multiple P-C bridging	5
Panacinar or multiacinar necrosis	6
(C) Focal (spotty) lytic necrosis, apoptosis and focal inflammation	
Absent	0
One focus or less per x10 objective	1
Two to four foci per x10 objective	2
Five to ten foci per x10 objective	3
More than ten foci per x10 objective	4
(D) Portal inflammation	
Absent	0
Mild, some or all portal areas	1
Moderate, some or all portal areas	2
Moderate/marked, all portal areas	3
Marked, all portal areas	4
Staging	
No fibrosis	0
Portal fibrosis, with or without short fibrous septa	1
Fibrous septa	2
Transition to cirrhosis	3
Cirrhosis, probable or definite	4

Table 2



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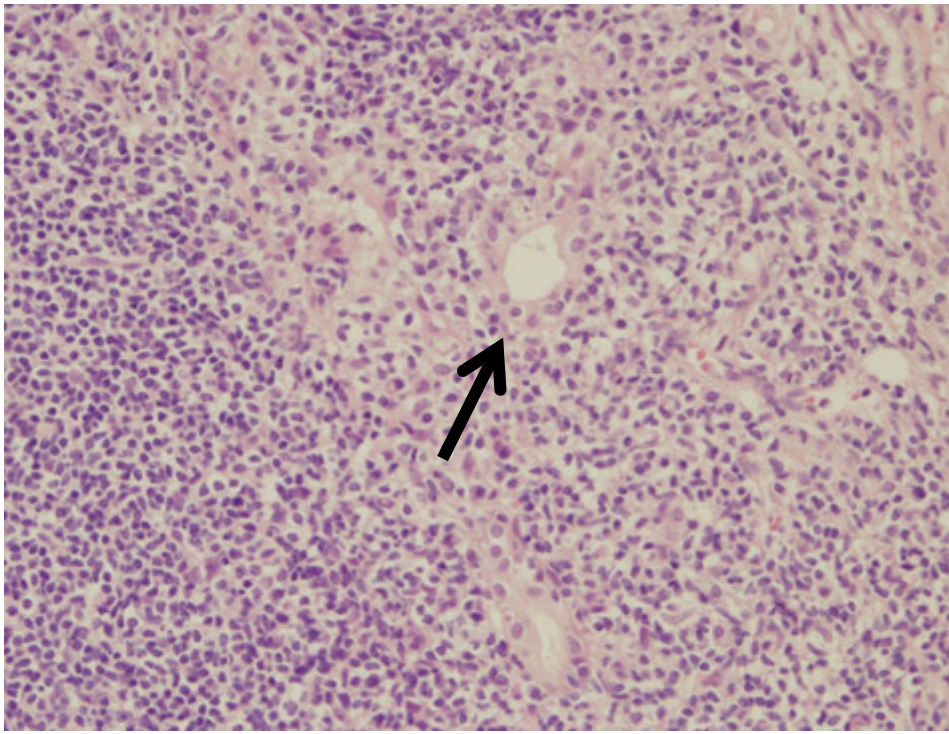
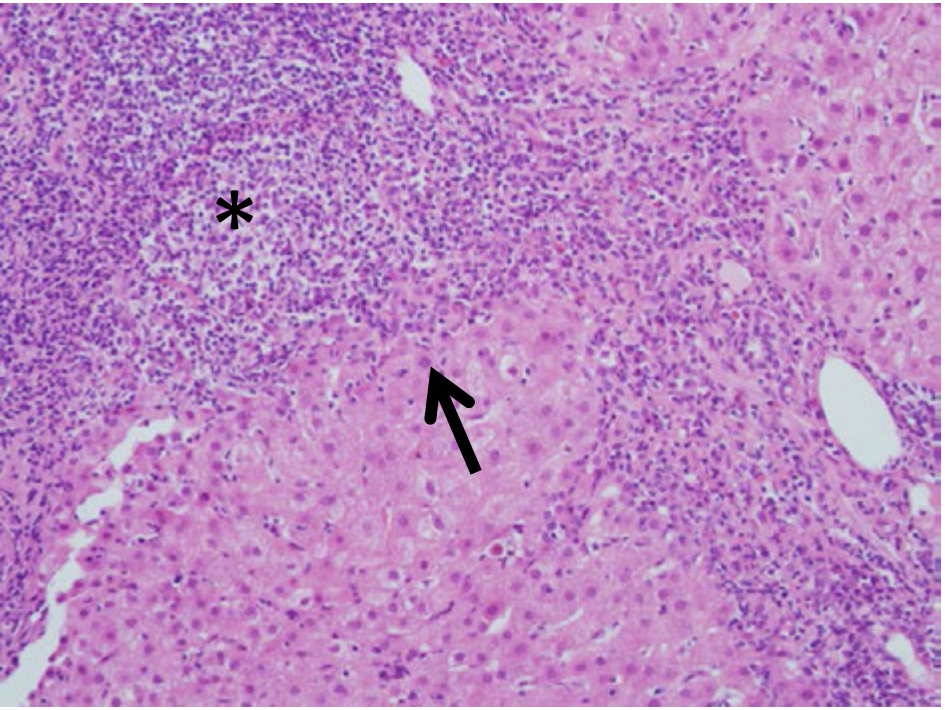
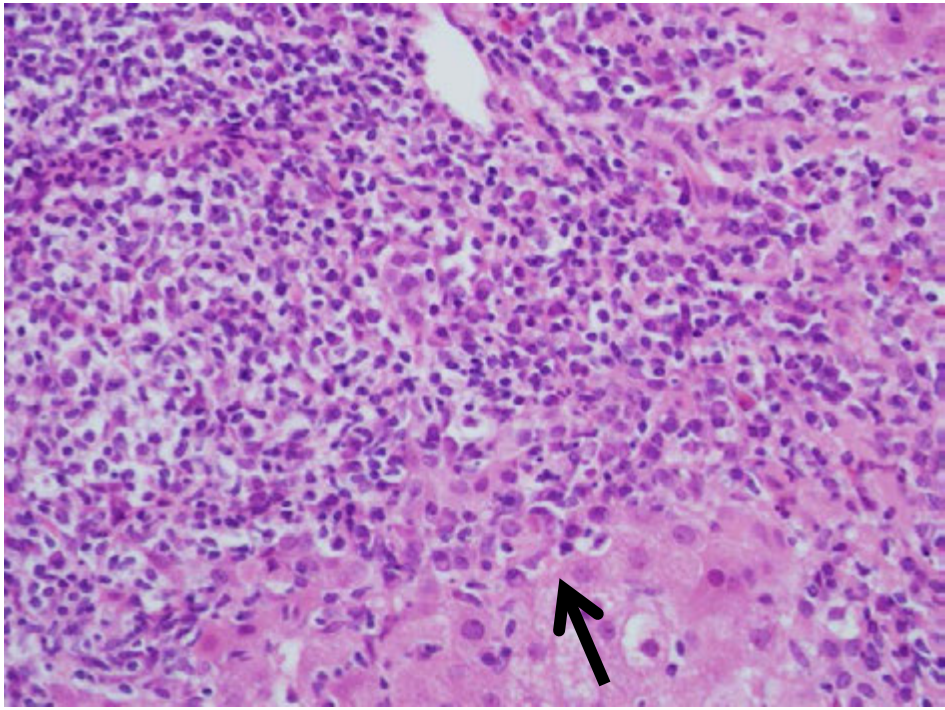


B

Fig.1





A

B

Fig.2

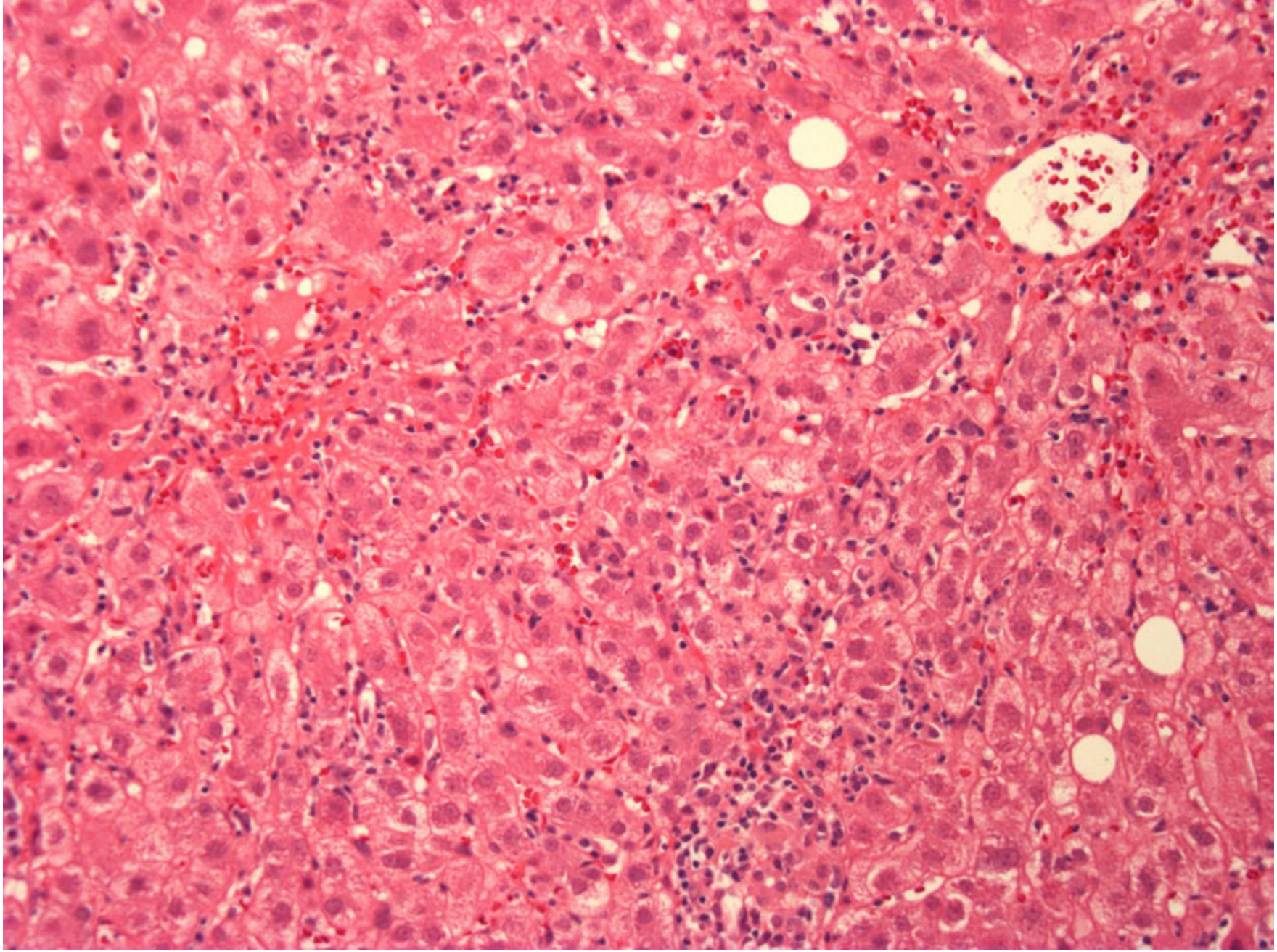
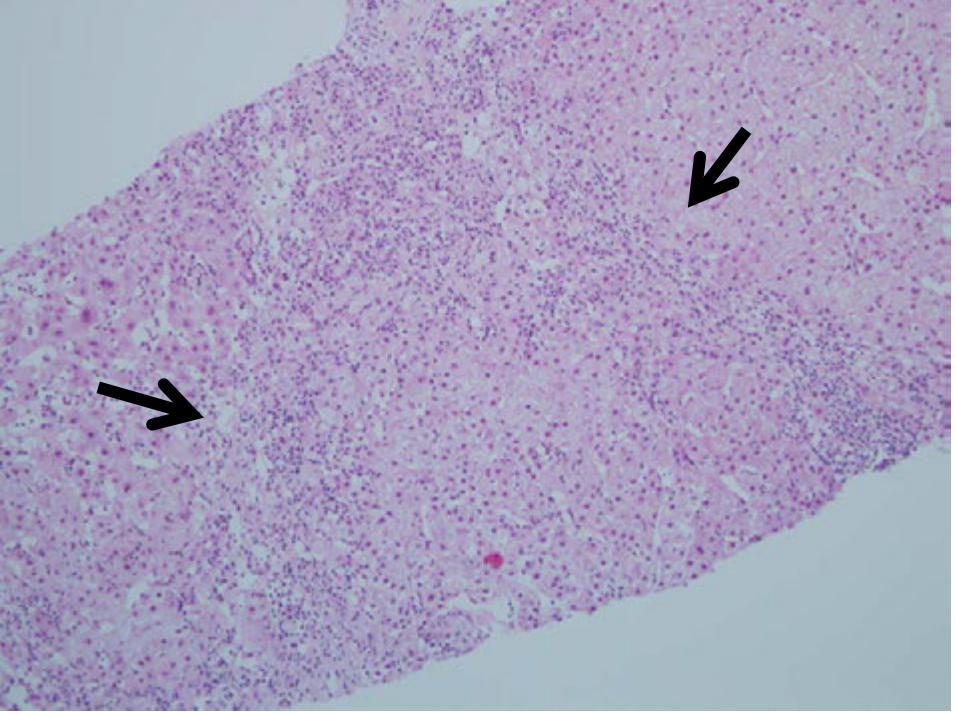


Fig.3



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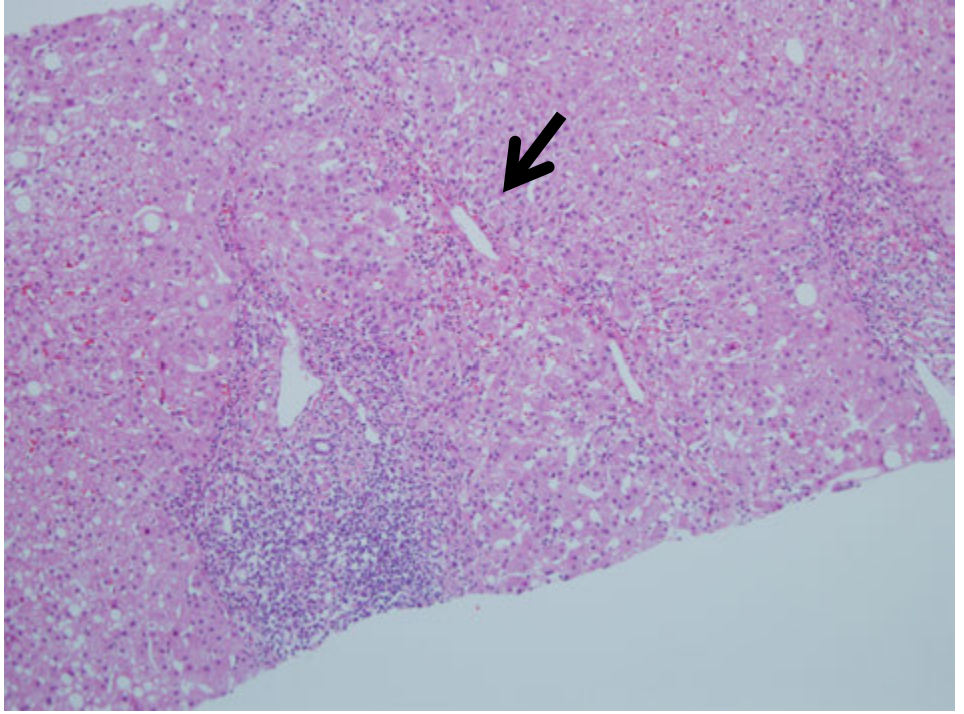

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Fig.4

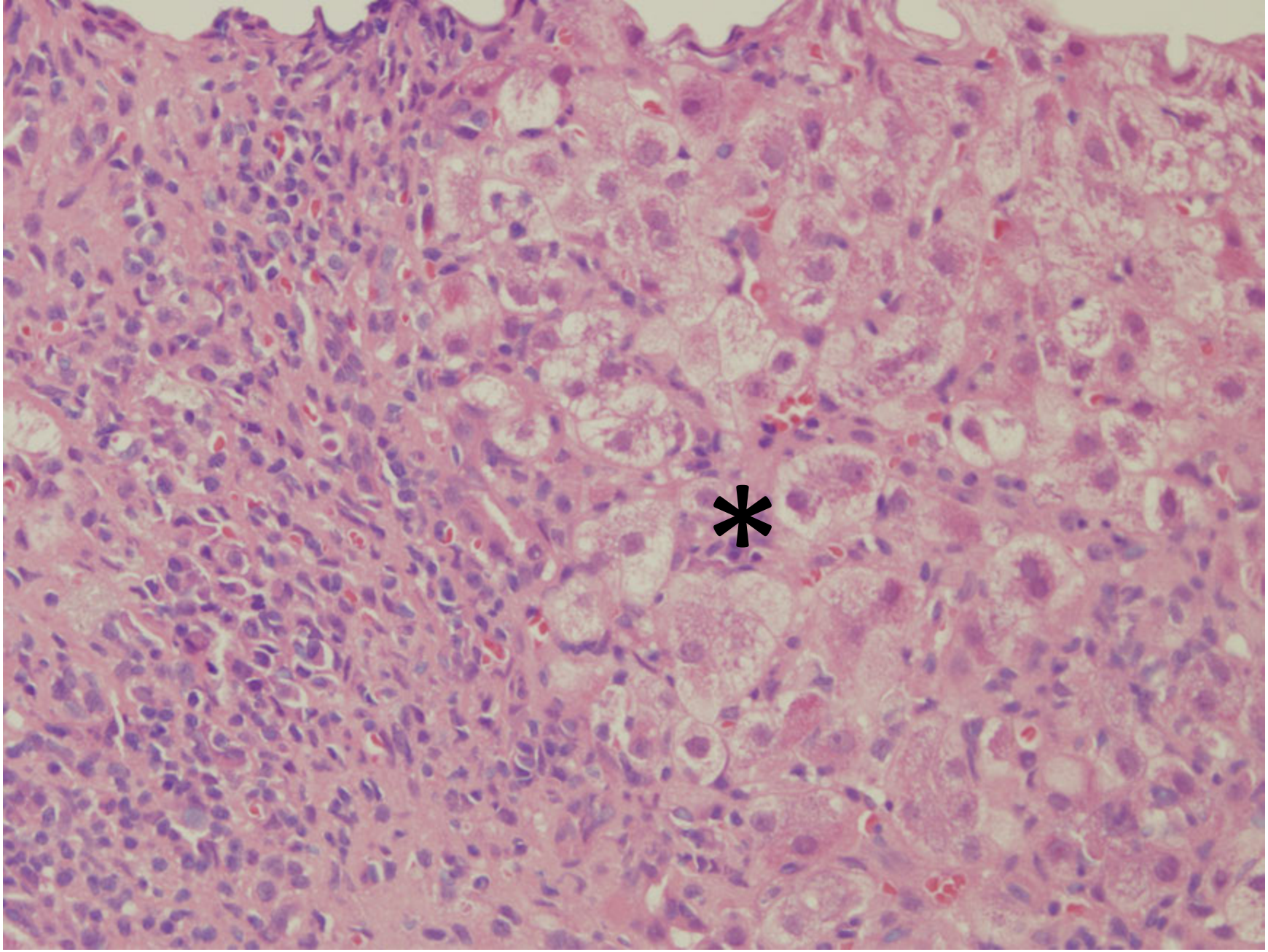


Fig.5

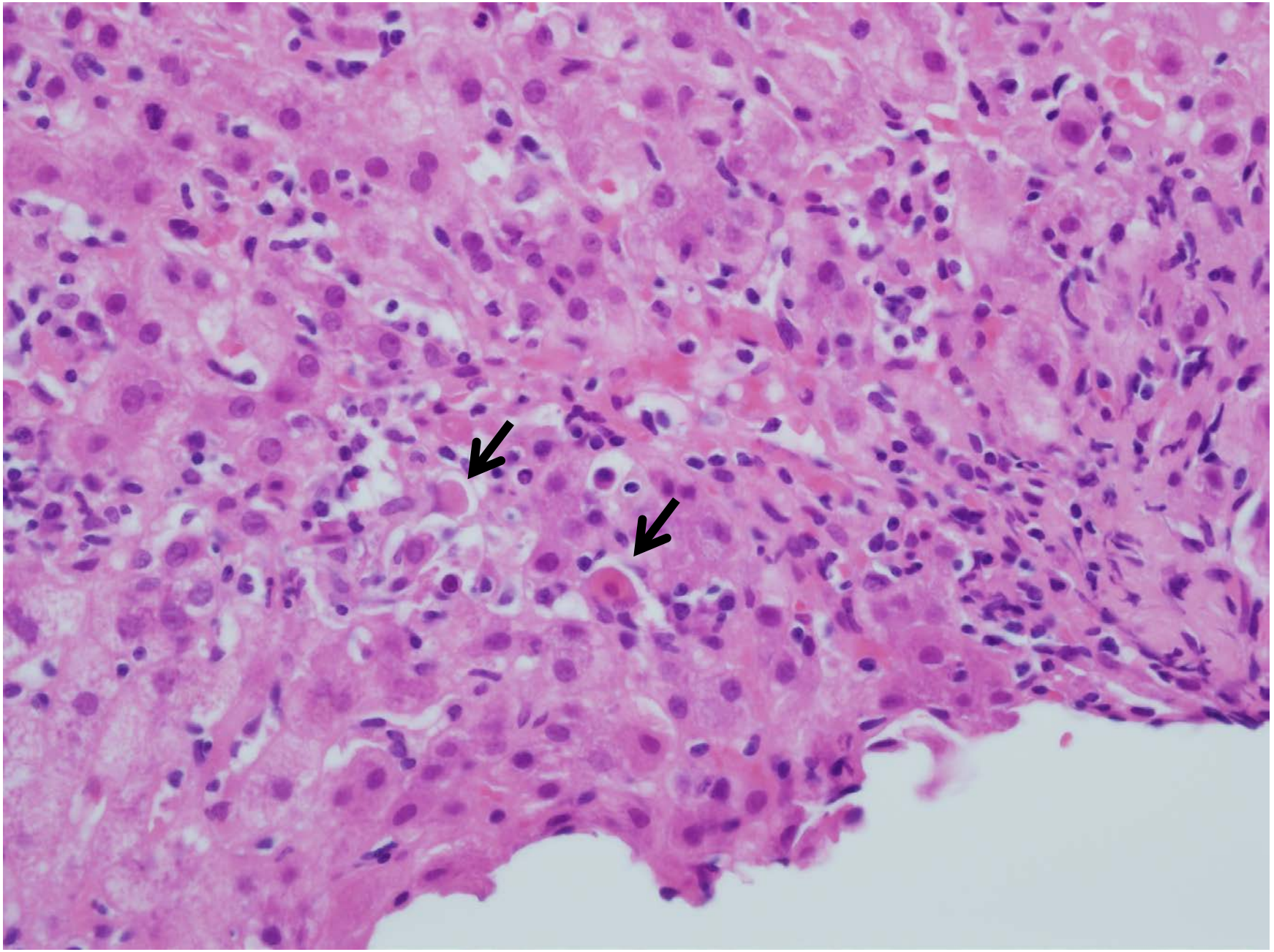


Fig.6

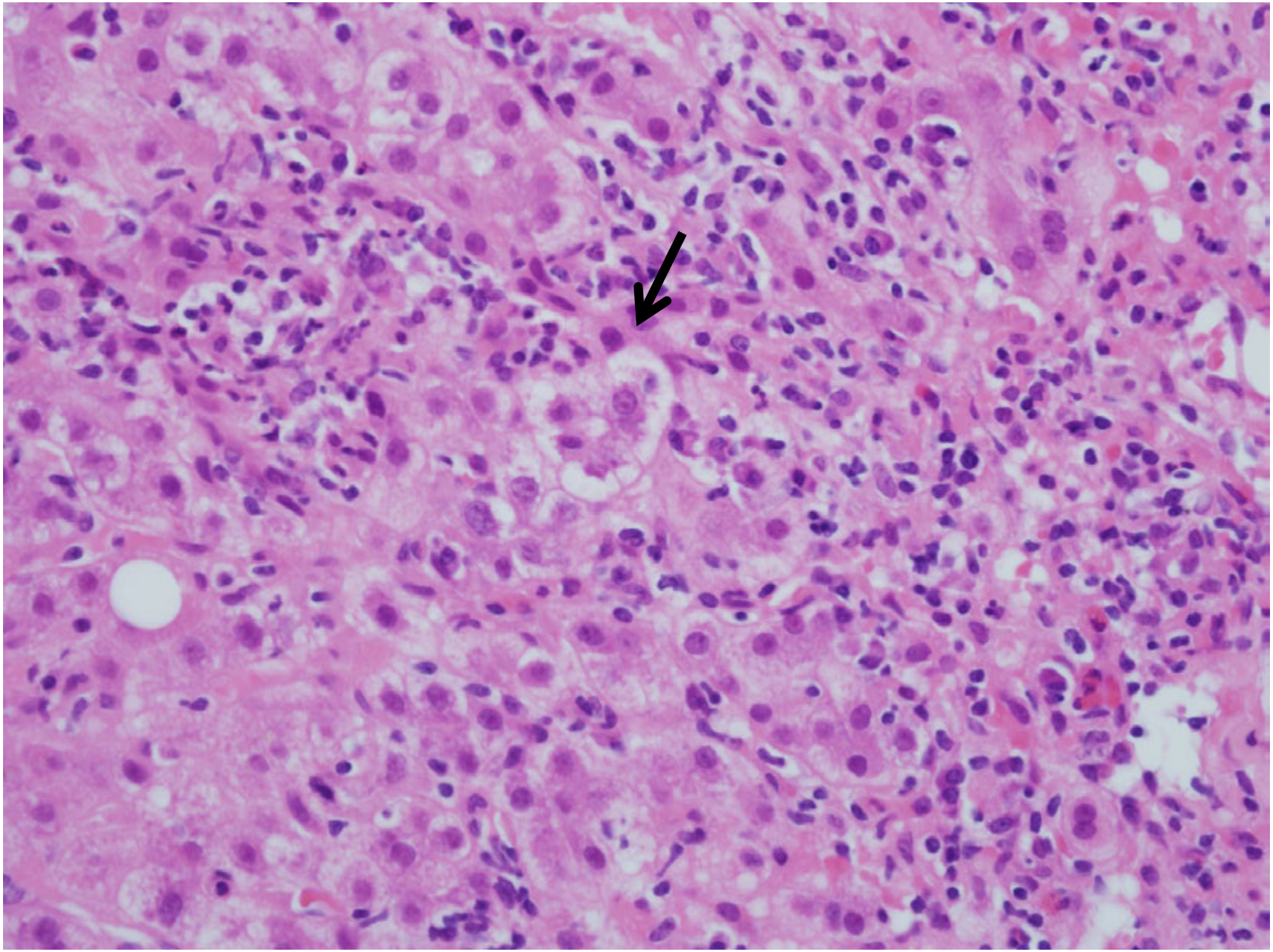
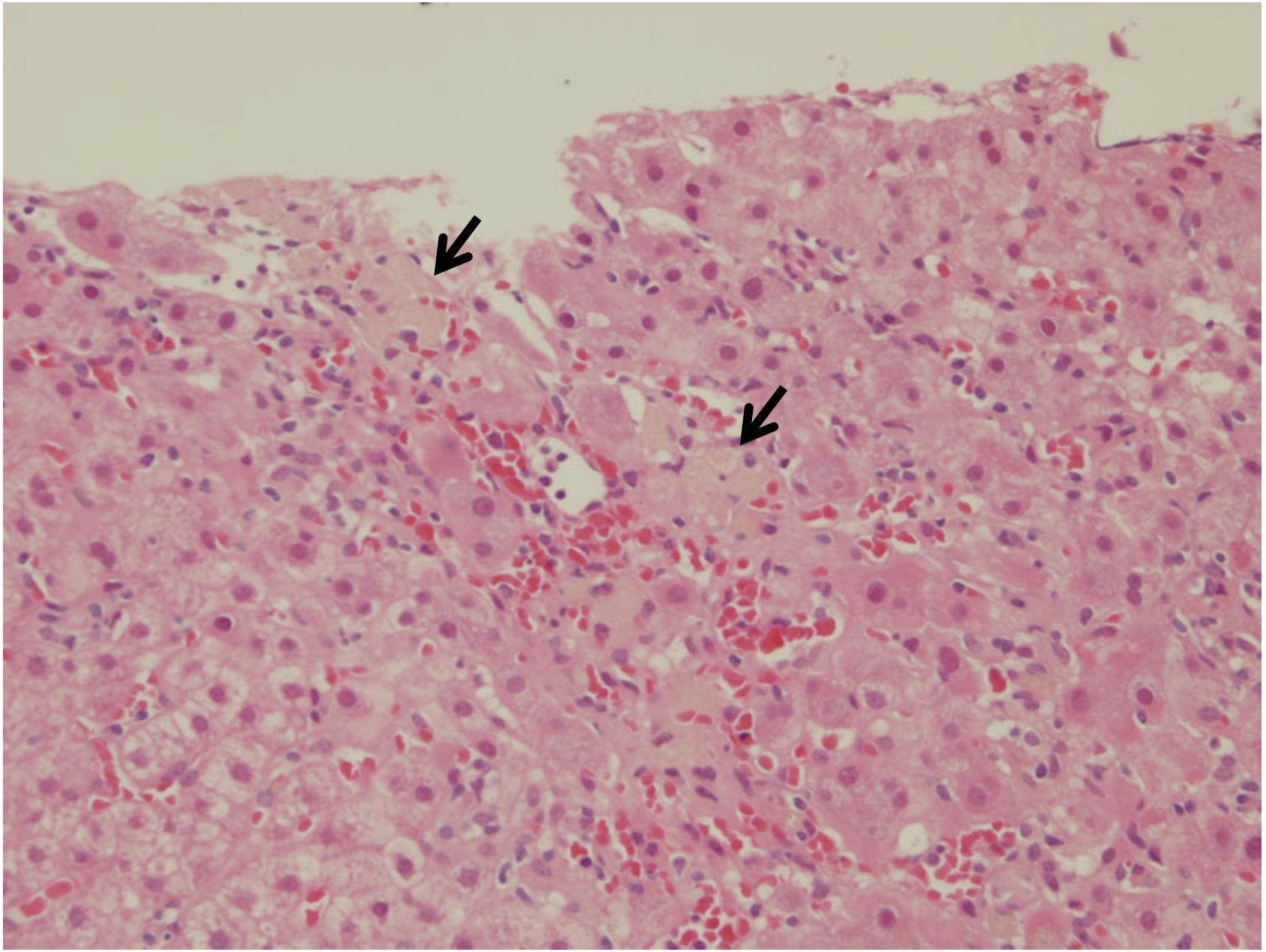


Fig.7



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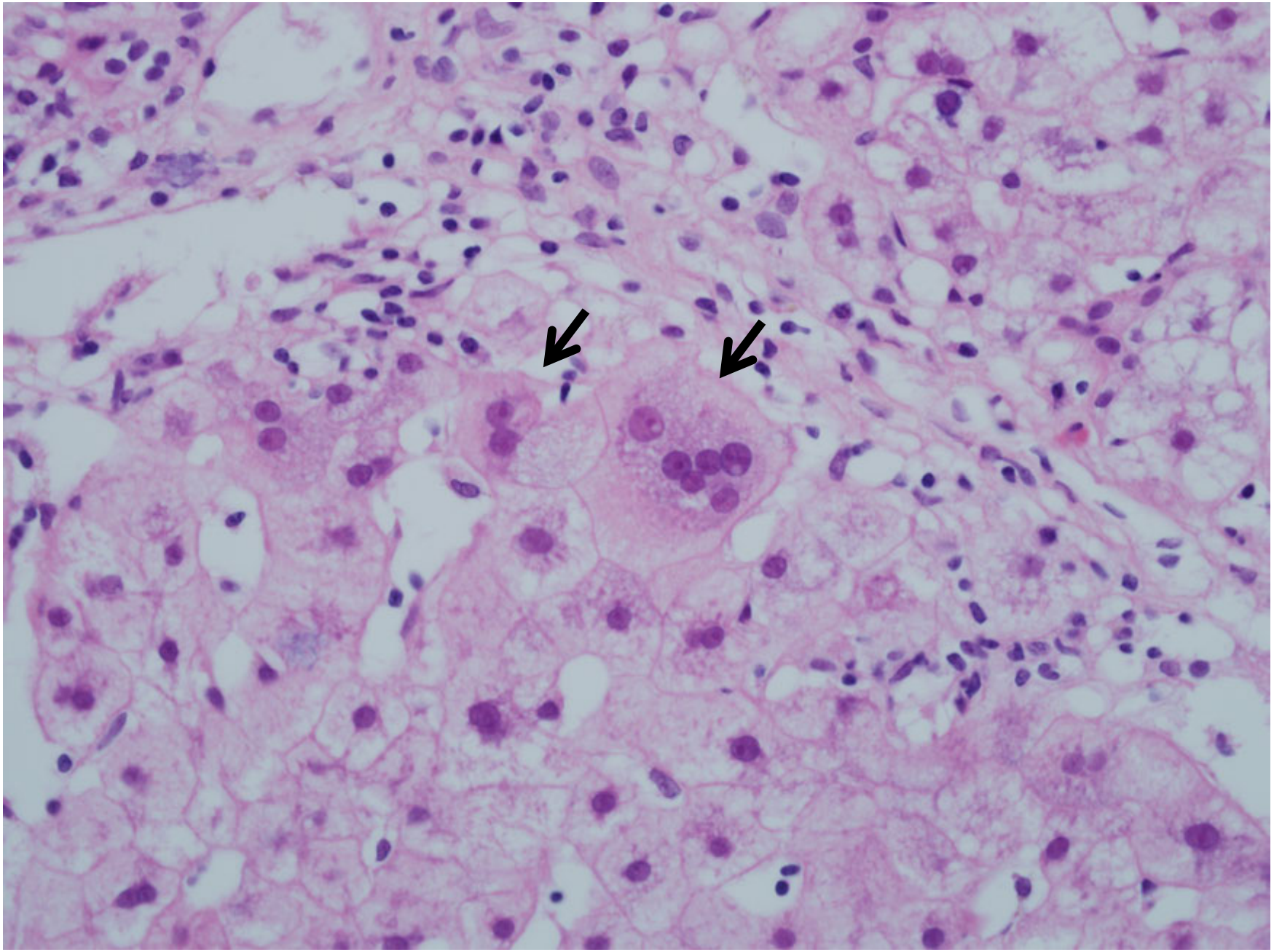


Fig.9

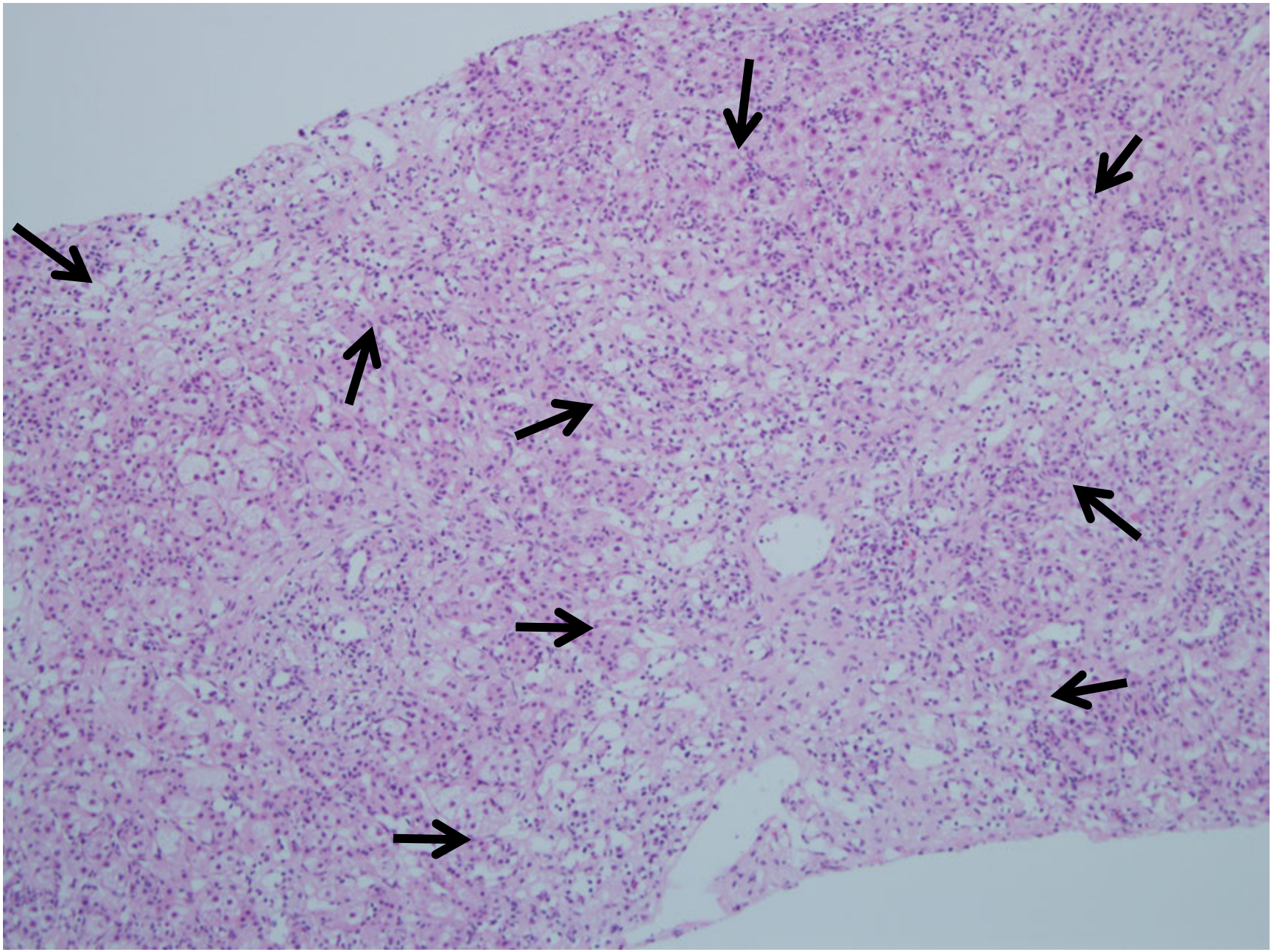
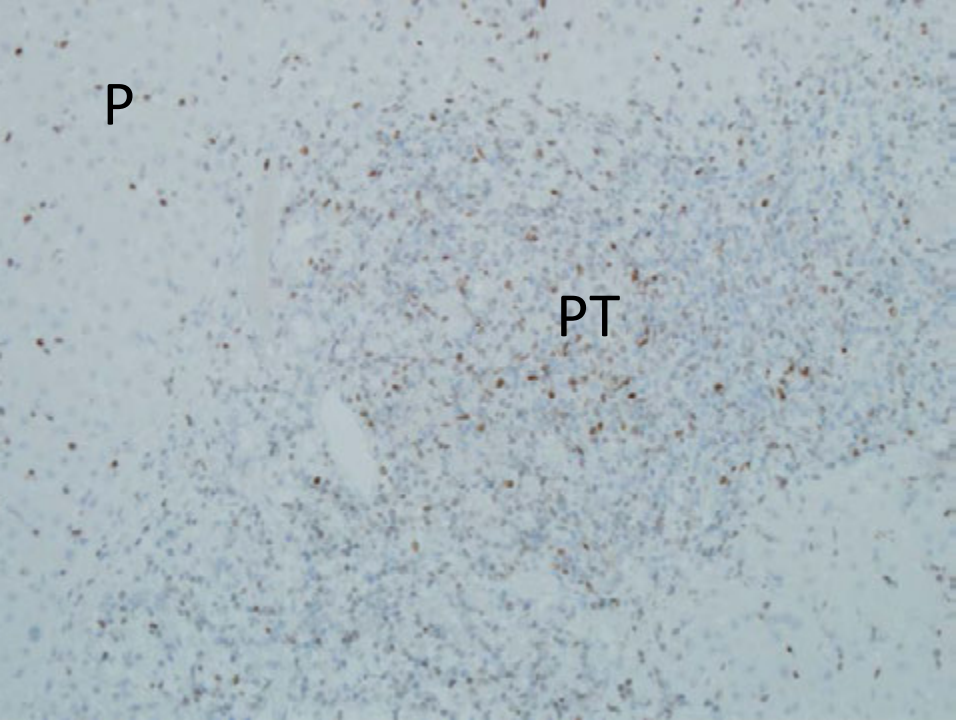


Fig.10



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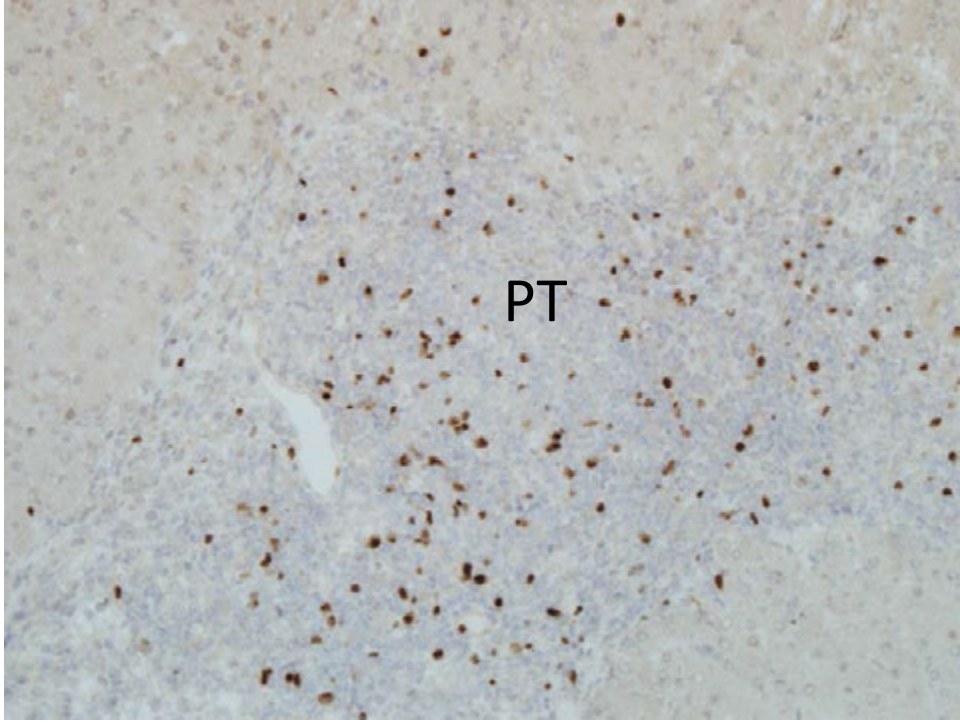

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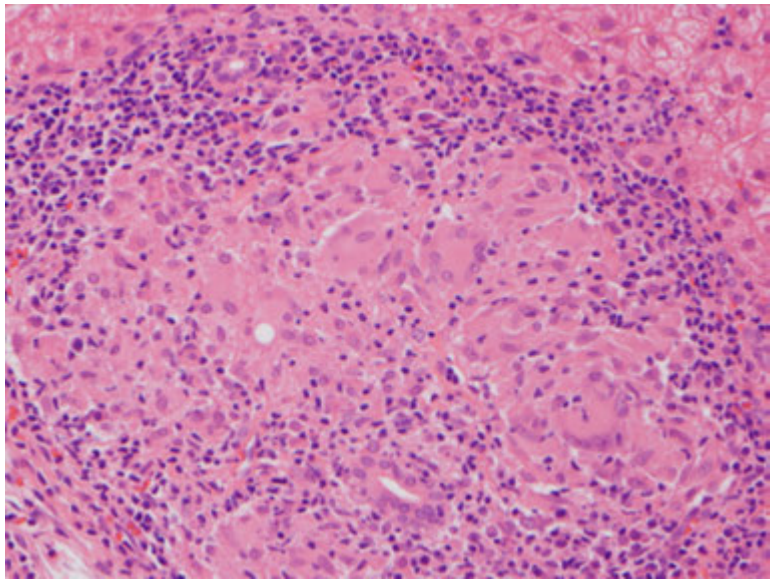
Fig.11



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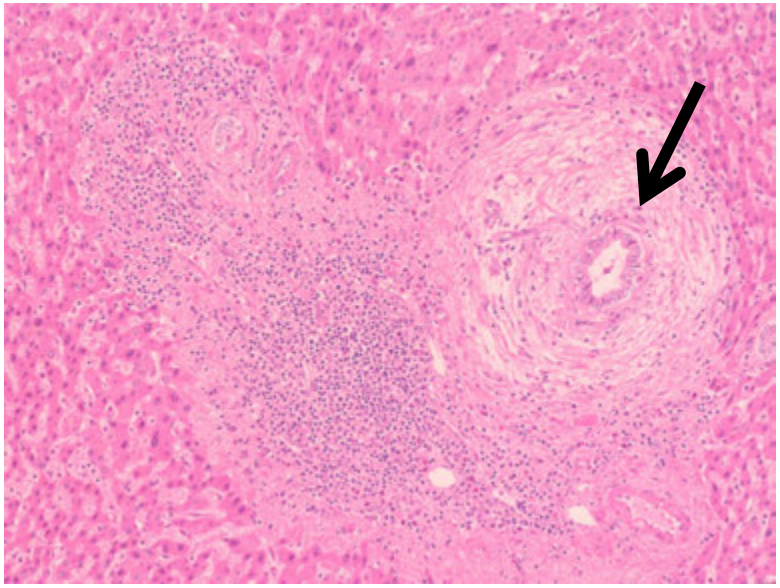

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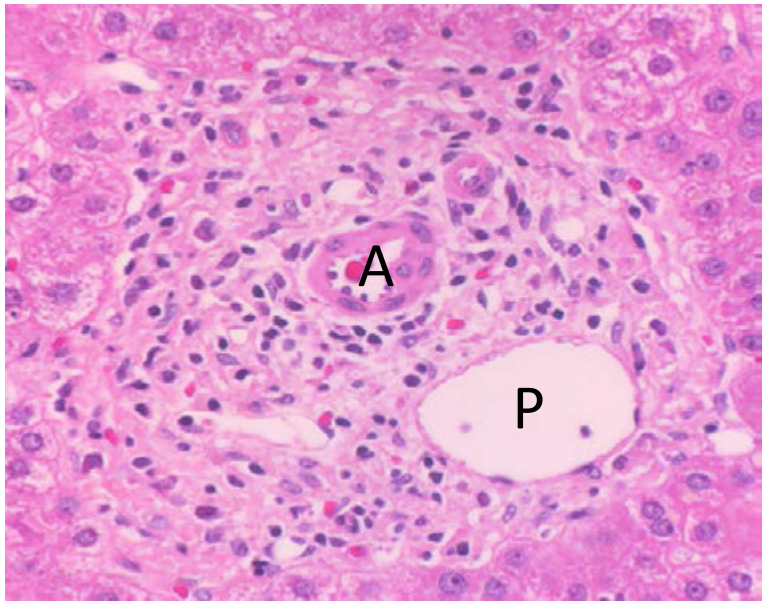

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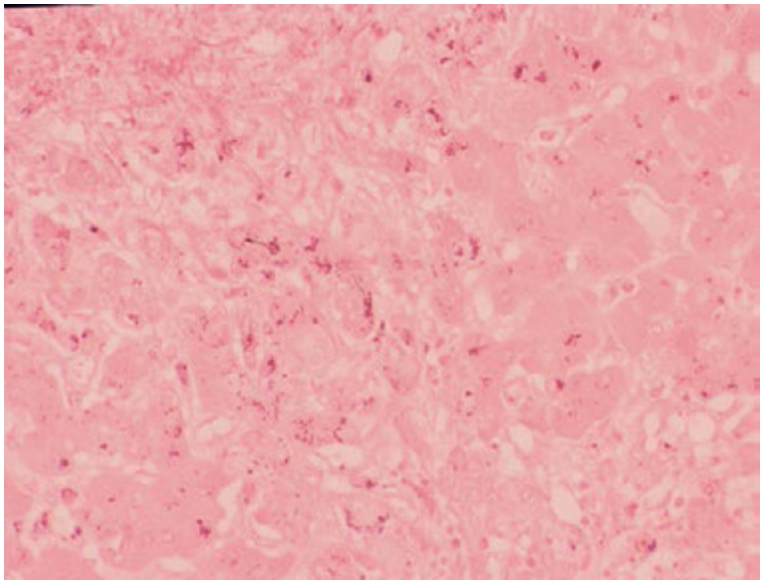


D

Fig.12

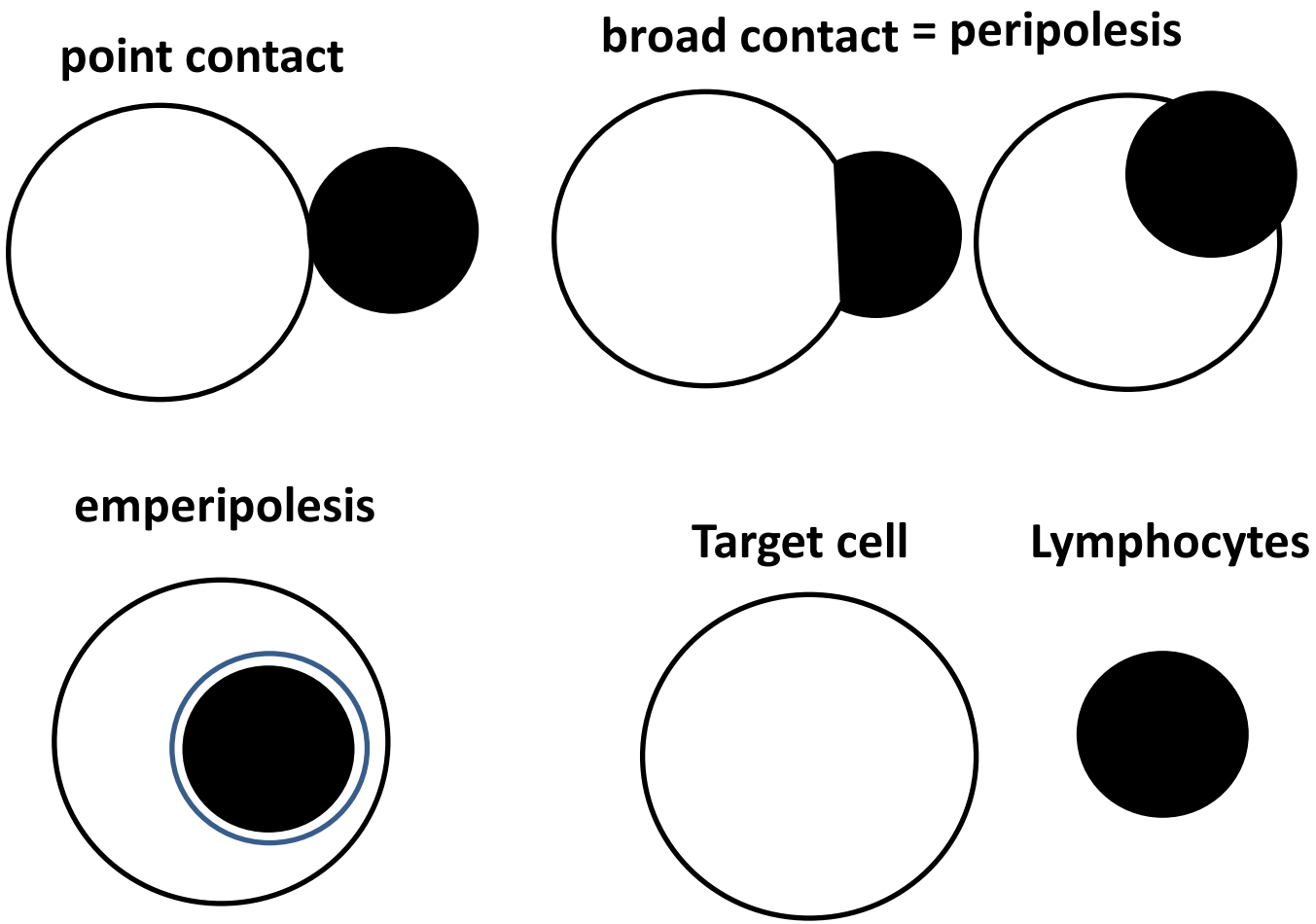
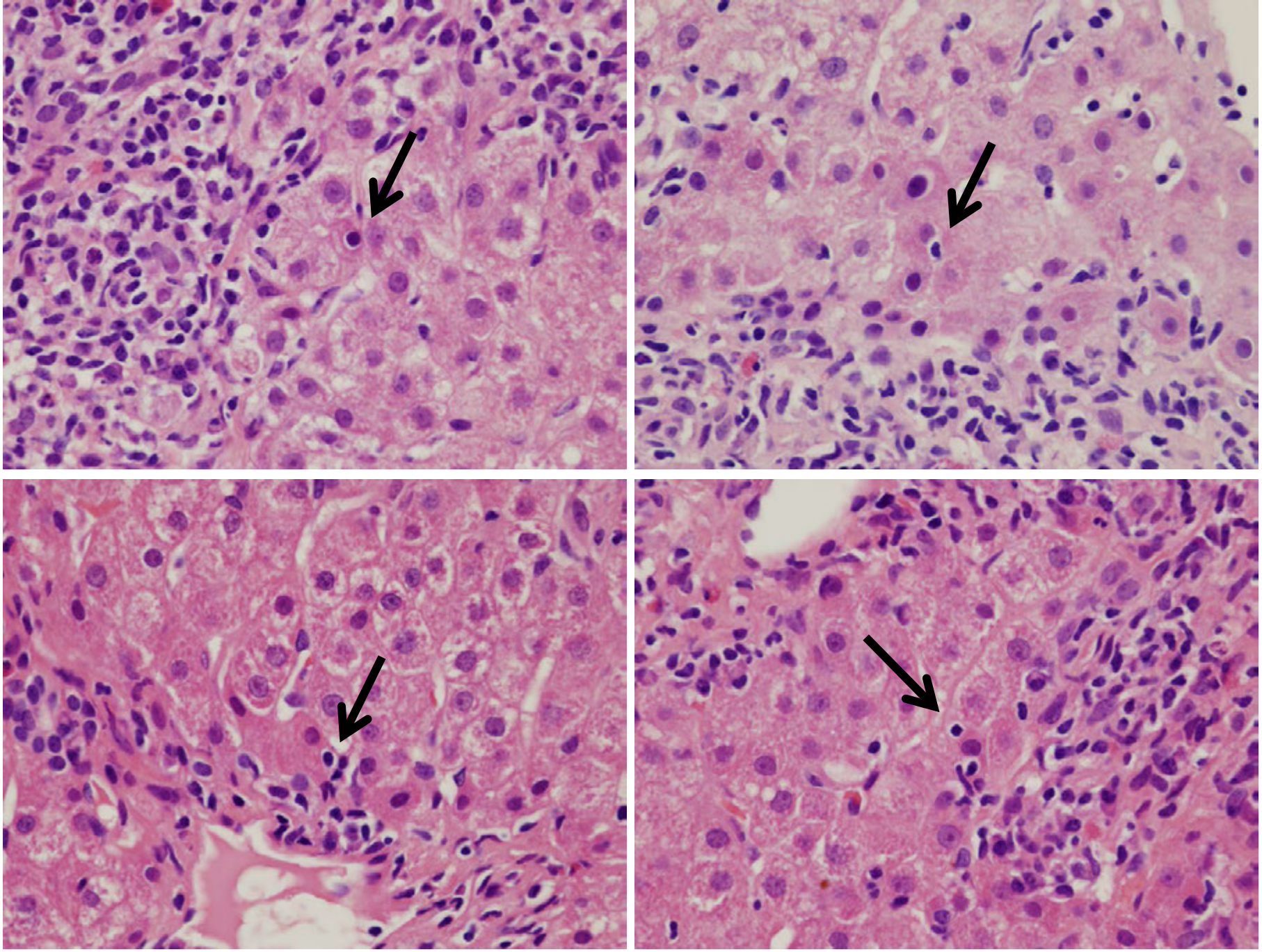

point contact
broad contact = peripolesis
emperipolesis
Target cell
Lymphocytes

Fig.13



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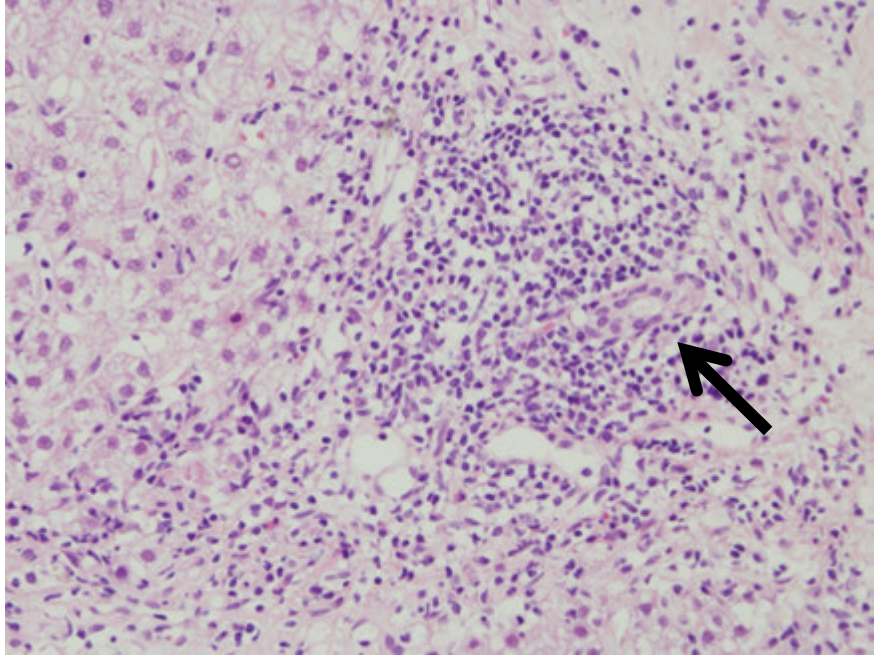

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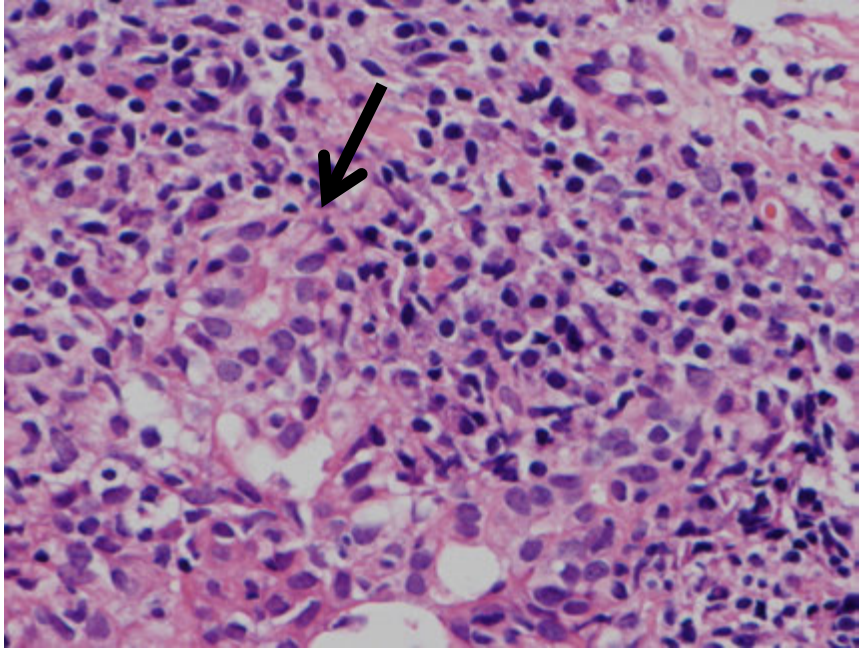

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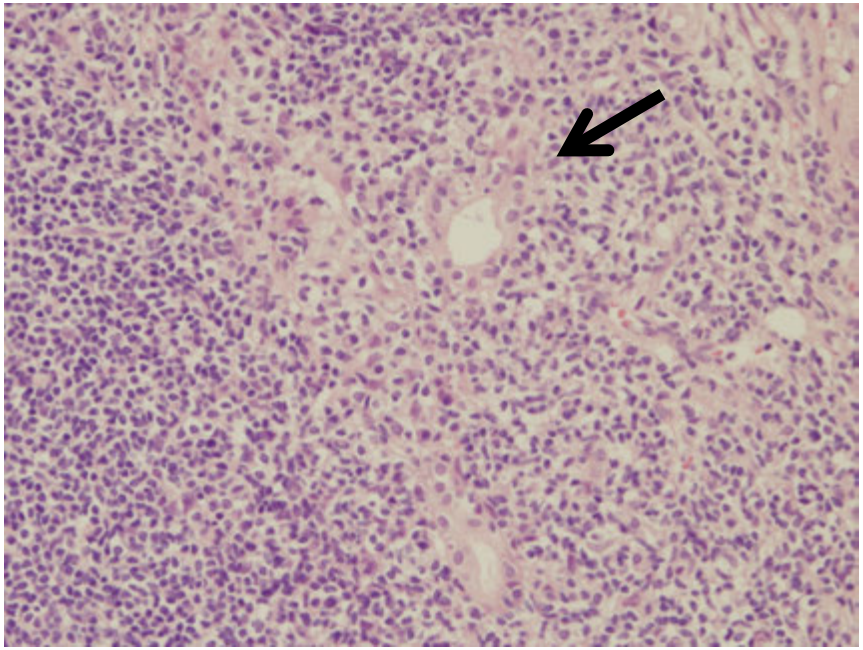

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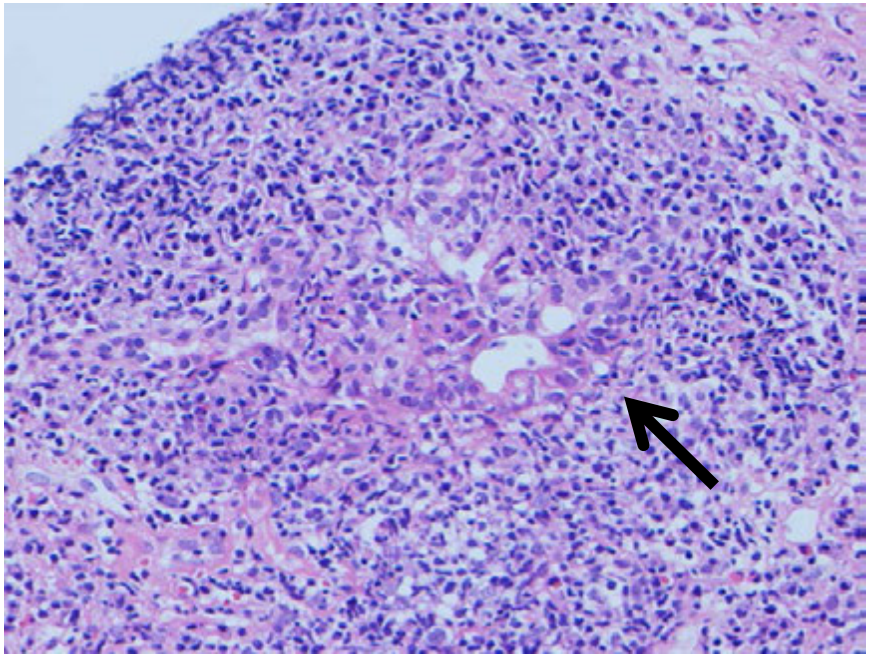

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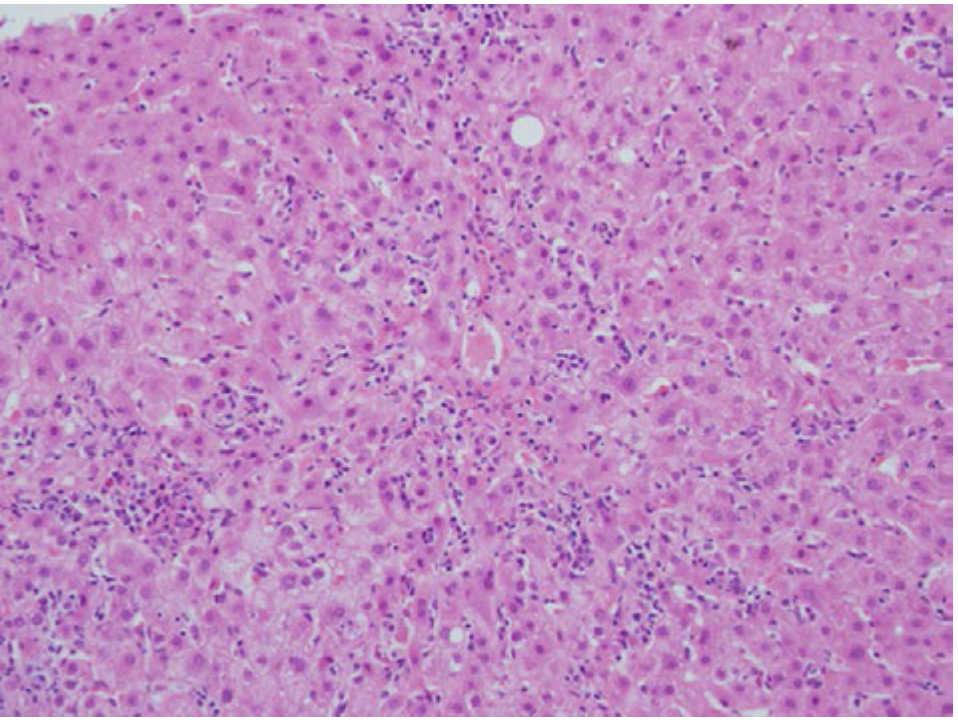
Fig.15



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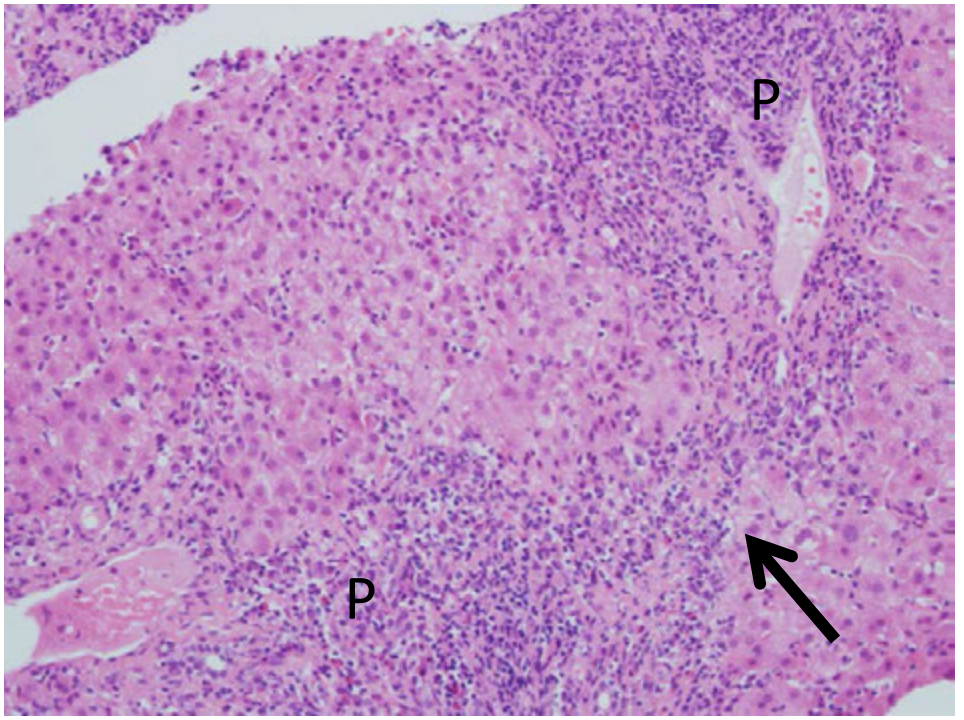

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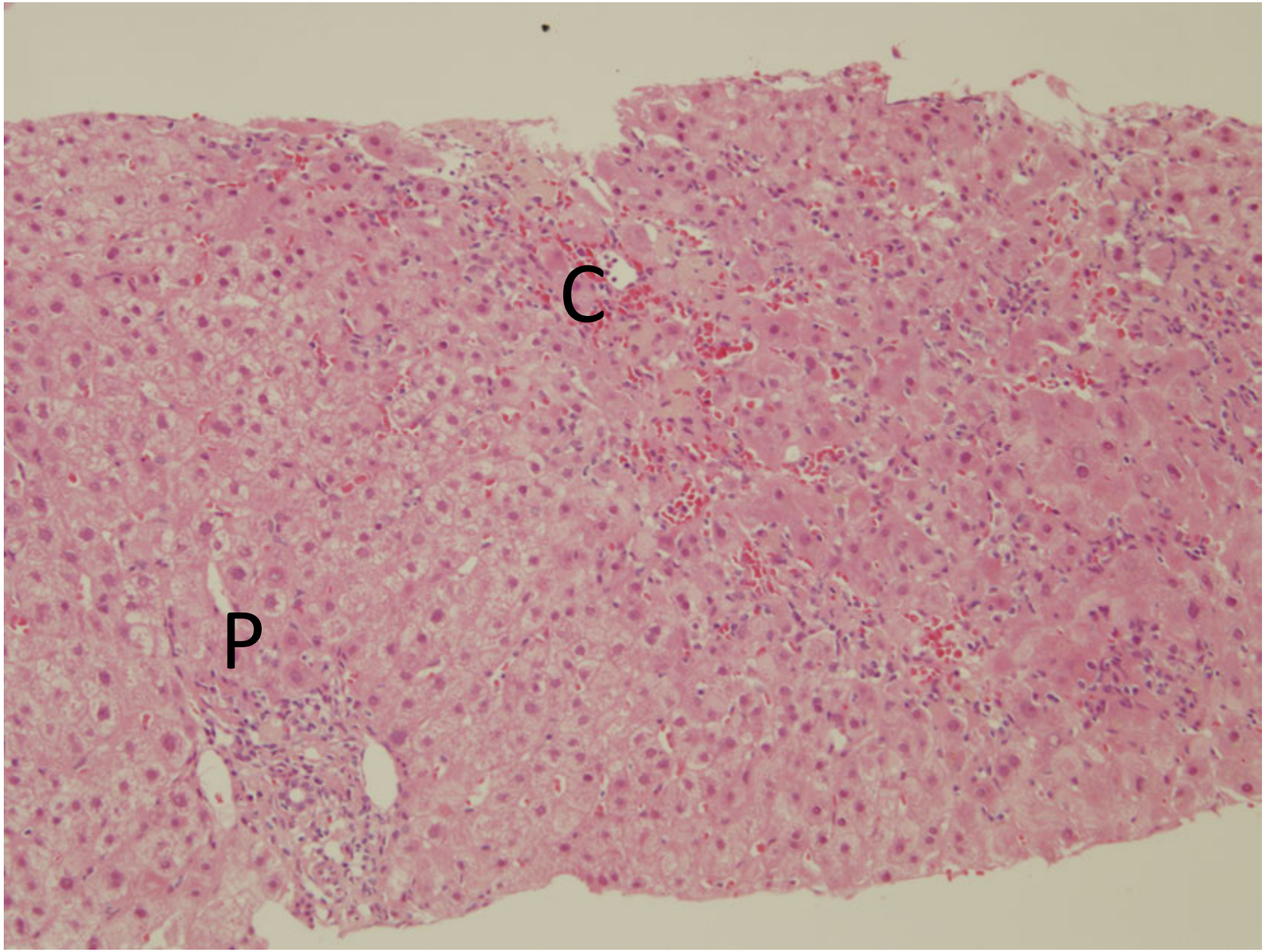
Fig.16



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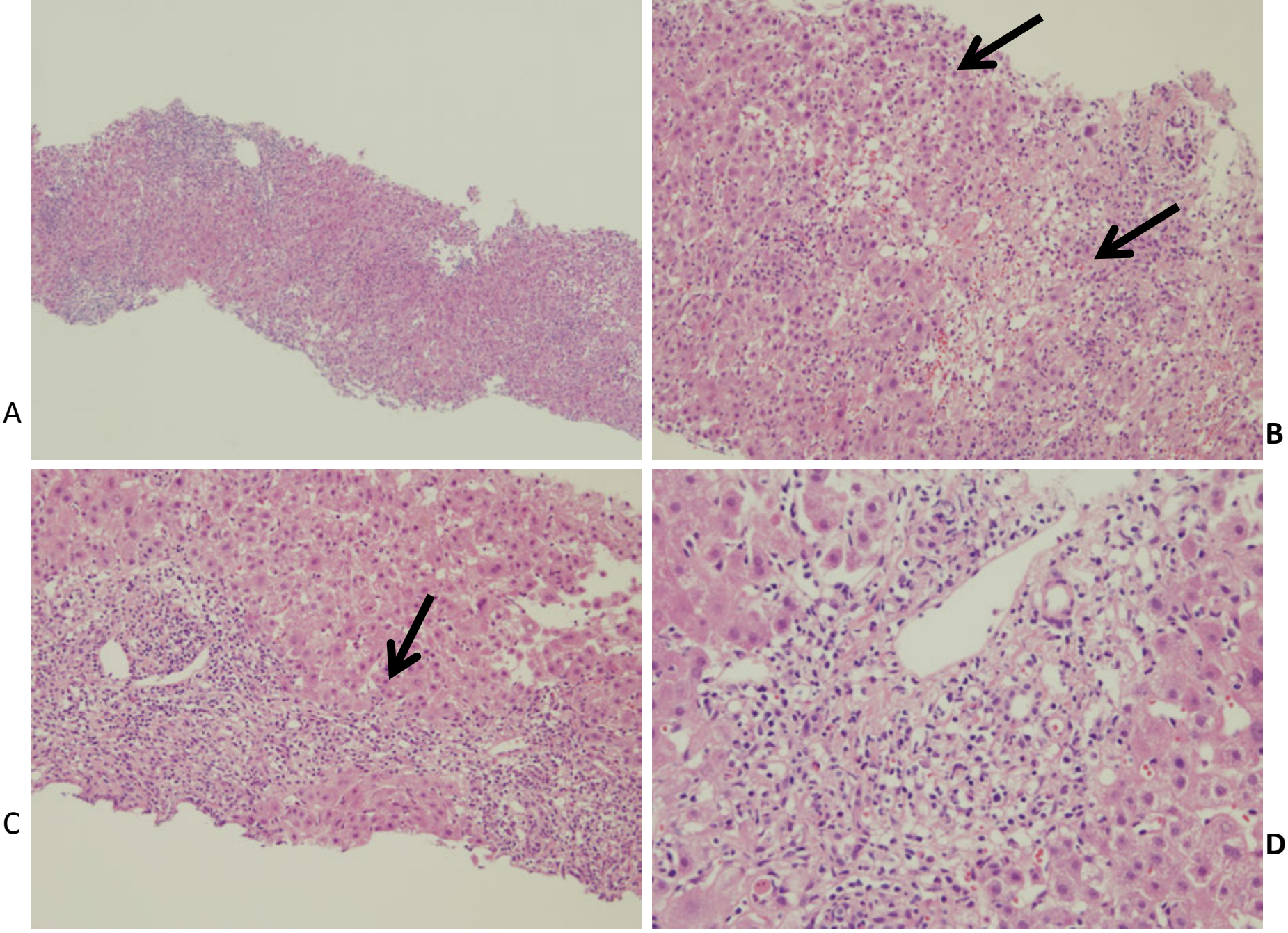

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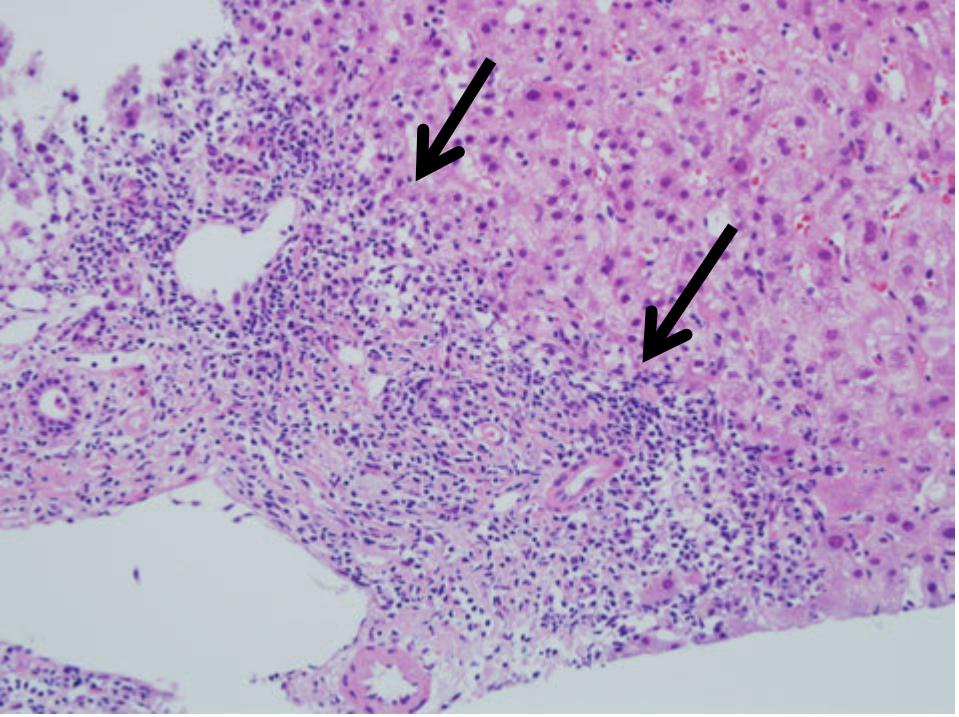

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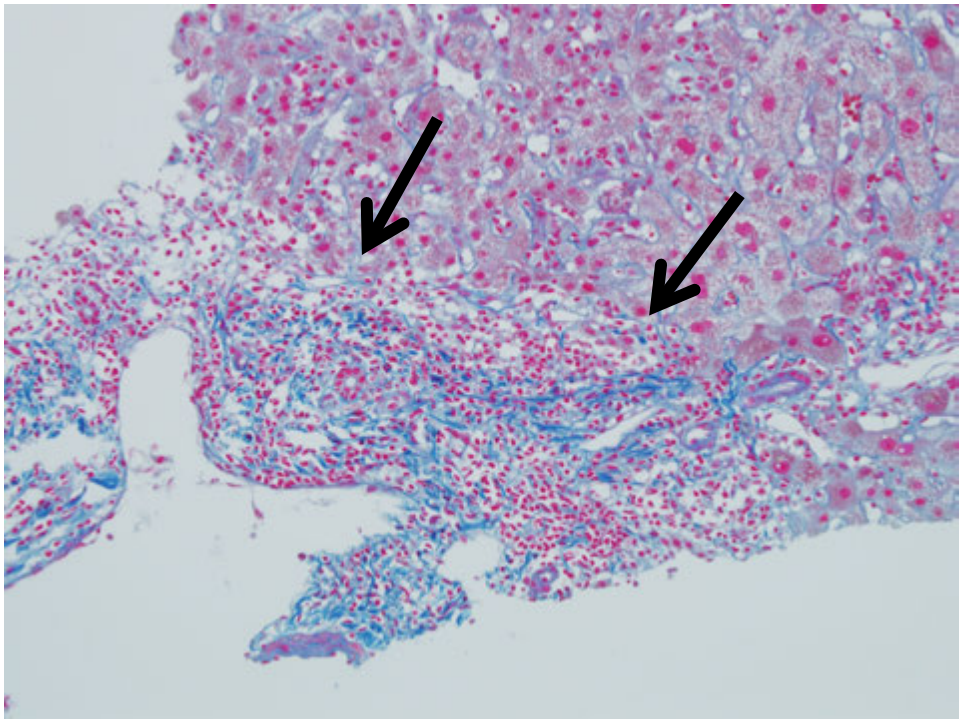

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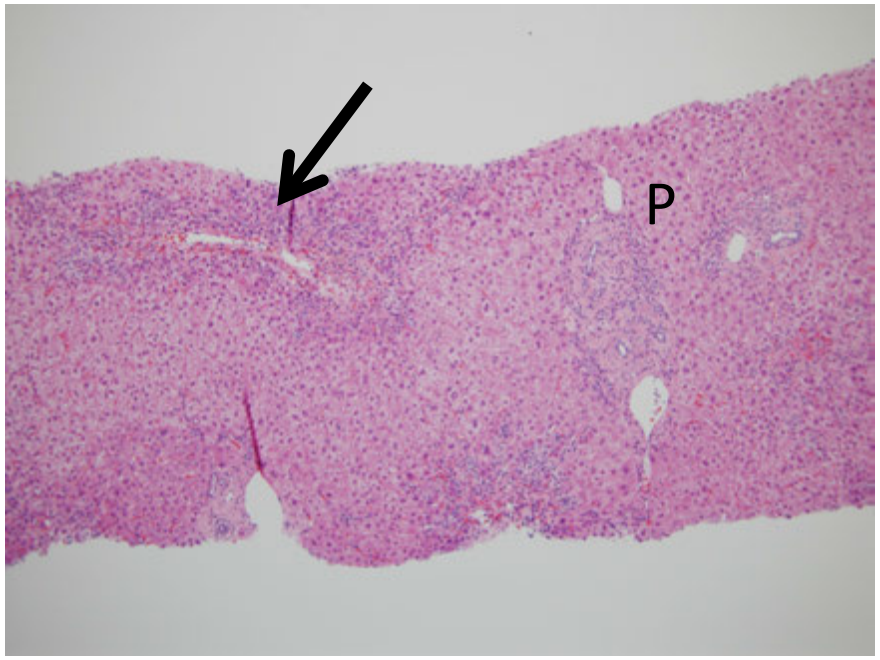
Fig.19



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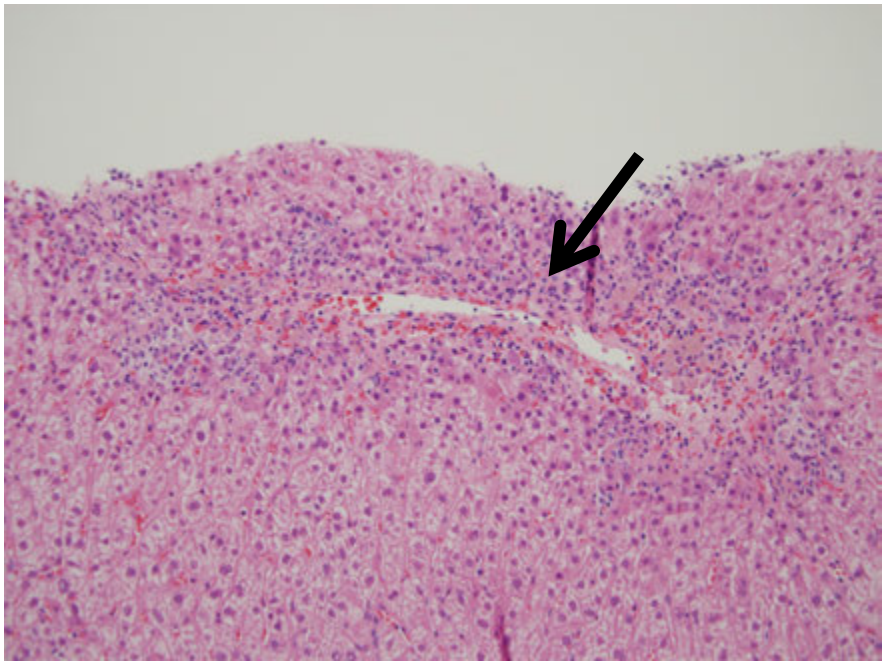

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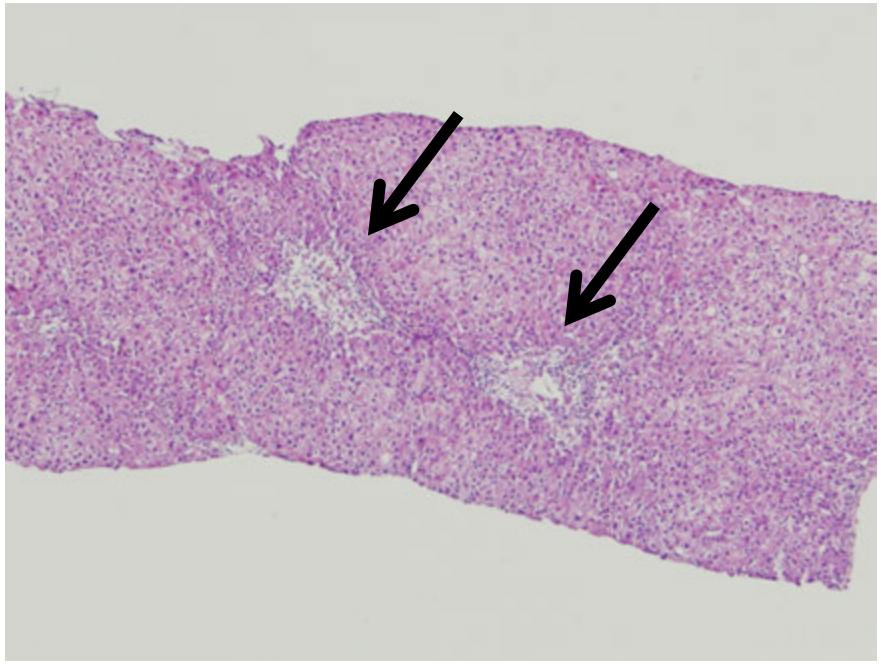

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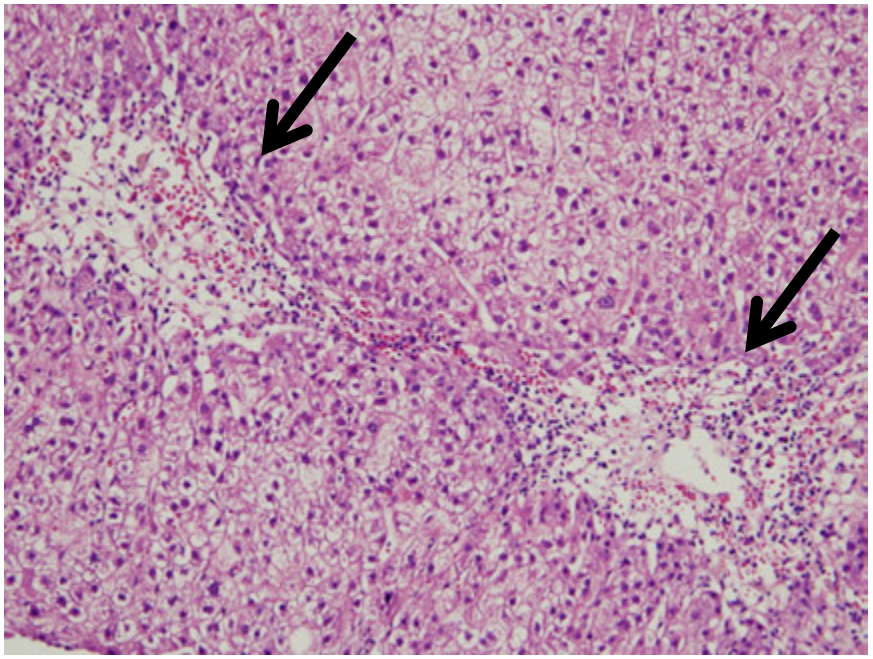

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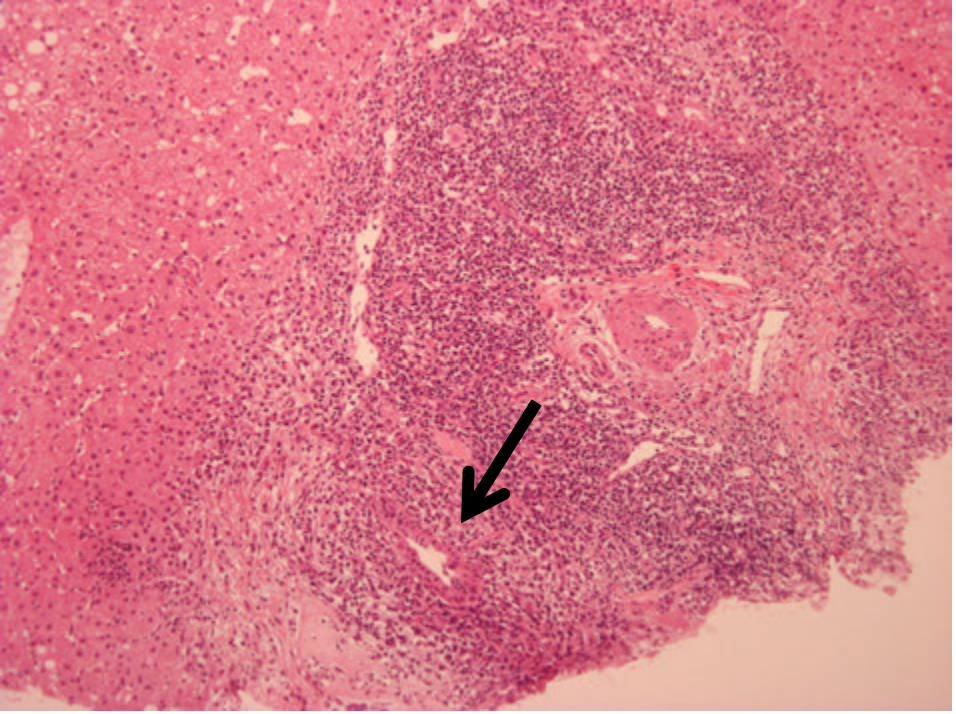
Fig.20



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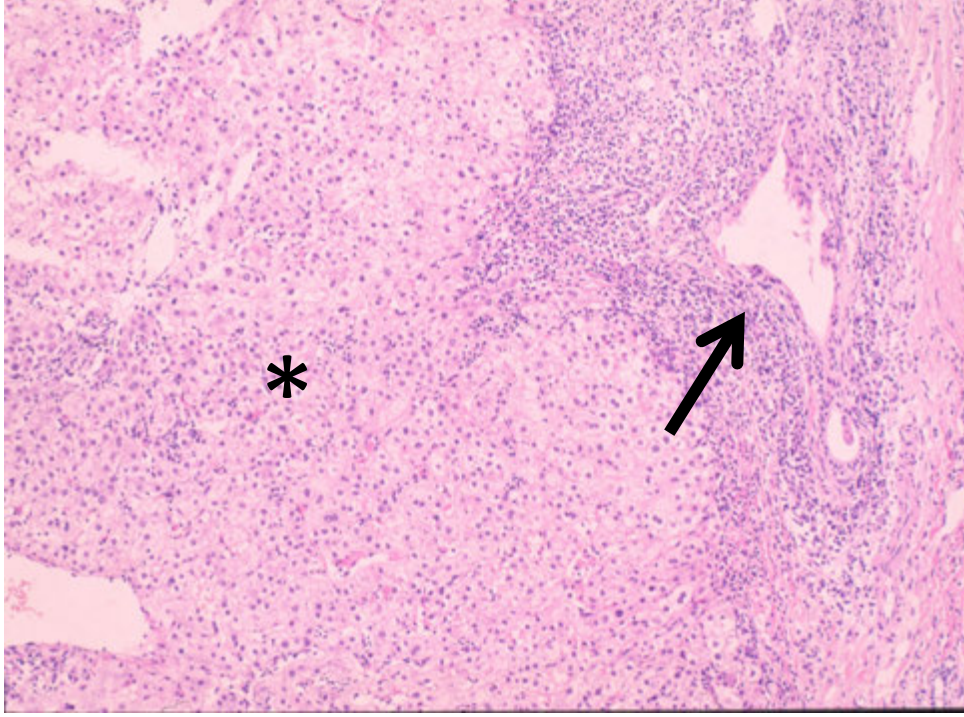

B

Fig.21