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Consensus Recommendations for Histological Criteria of Autoimmune Hepatitis from the International AIH Pathology Group

Results of a workshop on AIH histology hosted by the European Reference Network on Hepatological Diseases and the European Society of Pathology

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Abbreviations

AIH	Autoimmune Hepatitis
PBC	Primary Biliary Cholangitis
DILI	Drug-induced liver injury
MAD	Mean Absolute Deviation
IgG	Immunoglobulin G
EBV	Epstein-Barr Virus
CMV	Cytomegalovirus

mHAI	Modified Histological Activity Index
SLA/LP	Soluble Liver Antigen/Liver Pancreas Antigen
IAIHG	International Autoimmune Hepatitis Group
PSC	Primary Sclerosing Cholangitis
NAFLD	Non-alcoholic Fatty Liver Disease
NASH	Non-alcoholic steatohepatitis

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Data Availability Statement

Data available on request from the authors.

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Abstract

Background & Aims:

Diagnostic histological criteria for autoimmune hepatitis (AIH) have not been clearly established. Previously published criteria focused mainly on chronic AIH, in which inflammatory changes mainly occur in portal/periportal regions and may not be applicable to acute presentation of AIH, in which inflammatory changes are typically predominantly lobular in location. International consensus criteria for the diagnosis and assessment of disease severity in both acute and chronic AIH are thus urgently needed.

Methods:

Seventeen expert liver pathologists convened at an international workshop and subsequently used a modified Delphi panel approach to establish consensus criteria for the histopathological diagnosis of AIH.

Results:

The consensus view is that liver biopsy should remain standard for diagnosing AIH. AIH is considered likely, if there is a predominantly portal lymphoplasmacytic hepatitis with more than mild interface activity and/or more than mild lobular hepatitis in the absence of histological features suggestive of another liver disease. AIH is also considered likely if there is predominantly lobular hepatitis with or

without centrilobular necroinflammation and at least one of the following features: portal lymphoplasmacytic hepatitis, interface hepatitis or portal-based fibrosis, in the absence of histological features suggestive of another liver disease. Emperipolesis and hepatocellular rosettes are not regarded as being specific for AIH.

Conclusions:

The criteria proposed in this consensus statement provide a uniform approach to the histological diagnosis of AIH, which is relevant for patients with an acute as well as a chronic presentation and to more accurately reflect the current understanding of liver pathology in AIH.

Electronic word count of the abstract: 250

Key words: autoimmune hepatitis; histology; portal hepatitis; lobular hepatitis.

Lay summary:

Autoimmune hepatitis (AIH) is an autoimmune liver disease that may present as an acute or chronic inflammation of the liver. Microscopic histological assessment of a liver biopsy is required for establishing the diagnosis of AIH. Diagnostic criteria for evaluating liver biopsies from patients with a suspected diagnosis of AIH were proposed in the 1990s but need re-evaluation since their specificity is still unclear. This consensus statement reviews the former histological criteria of AIH and proposes updated criteria to be used for the diagnosis of AIH and for the assessment of the severity of liver inflammation.

Introduction

Autoimmune hepatitis (AIH) is a rare disease but is being diagnosed with increasing frequency around the world.[1] The clinical picture is very heterogeneous. The disease can start in infancy, but can also manifest in the 8th or 9th decade of life for the first time.[2-4] Similarly, the disease can manifest as asymptomatic mild disease coming to medical attention because of raised liver enzymes on a routine blood test, or present with an acute hepatitis or even acute liver failure.[5] Up to one third of all AIH patients have cirrhosis at the time of initial diagnosis because the disease had a subclinical, undetected course.[1] The wide spectrum of clinical presentations in combination with lack of specific or sensitive laboratory markers makes the diagnosis of AIH challenging even for experts, and has led to the use of scores to help in making the diagnosis.[2,3,6] Liver histology represents a central component of these scores, thus liver biopsy is considered mandatory in the diagnostic work-up of AIH in most guidelines published by international scientific societies.[4,7-9] There is no diagnostic biomarker for AIH and histopathology plays a key role in designating the diagnosis of AIH as definite, probable or unlikely. However, the histological criteria for making a diagnosis of AIH are largely based on old studies, and have neither been prospectively validated, nor agreed upon by international consensus.

AIH was initially described as a chronic disease. Indeed, the disease was called chronic autoimmune hepatitis as part of the spectrum of chronic active hepatitis until 1993.[2] Inflammatory changes in the context of chronic AIH are characterised by predominantly portal-based lymphoplasmacytic inflammation associated with varying degrees of interface hepatitis (previously referred to as “piecemeal necrosis”). These early studies largely provided the basis for the histological criteria used in diagnostic scores.[3,6] Patients with an acute

presentation of AIH, typically have predominantly lobular-based inflammation which may be associated with centrilobular necrosis (central perivenulitis) and may lack the typical portal/periportal histological features of chronic hepatitis.[10-15] The scoring systems proposed for the histological diagnosis of chronic AIH are consequently inadequate in the setting of acute AIH. Such cases are often misclassified as drug-induced or toxic acute liver injury and the diagnosis of AIH may not be considered in the histopathological evaluation. As AIH patients would particularly benefit from the rapid institution of immunosuppressive treatment, recognition and accurate diagnosis of AIH presenting as acute hepatitis is of paramount importance.[16] Furthermore, recent evidence suggests that histological features such as hepatocellular rosettes and emperipolesis, which were considered to be necessary for classifying a case as “typical” AIH according to the 2008 simplified diagnostic criteria, can also be found in other inflammatory liver diseases such as viral hepatitis, primary biliary cholangitis (PBC) or drug-induced liver injury (DILI).[17-19] Hepatocyte rosettes are indicative of hepatocellular regeneration in the context of severe liver cell damage rather than pointing to a specific aetiology, while the pathophysiology of emperipolesis remains unclear. The aim of this study was to develop international consensus criteria for the diagnosis of AIH and for the assessment of disease severity in AIH, which could be applied to both acute and chronic presentations of the disease.

Material & Methods

Seventeen liver pathologists and two hepatologists (AWL and MS) with a special interest and expertise in AIH first met for a one-day workshop of the International AIH Pathology Group in Brussels, Belgium on January 21st 2020, for the revision of the histological criteria

of AIH, organised by the European Reference Network for Hepatological Diseases with the support of the European Society of Pathology. Panellists were selected based on their experience and international reputation in AIH histopathology. In preparation of the meeting, four pathologists (SH, DT, TK and SW) and two hepatologists (AWL and MS) designed an online survey of the standards, diagnostic criteria and histological grading of AIH with acute or chronic presentation. This survey was sent to all workshop participants. Based on the results of this survey and in-depth discussions that took place during the workshop, 25 statements and recommendations on AIH histopathology, including minimal requirements for adequate diagnosis, terminology determining the likelihood of the diagnosis of AIH, histological features applicable in the acute and chronic presentation of AIH, and scoring of disease activity (grading) and progression (staging) were formulated. The histological criteria and recommendations in this study refer to AIH occurring in the native liver and are not intended to be applied to the diagnosis of recurrent AIH in the liver allograft. After the workshop, each statement was rated by the 17 pathologists applying an online modified Delphi panel approach and analysed according to the RAND/ University of California Los Angeles (UCLA) appropriateness methodology manual.[20] The rating scale ranged from 1 (highly inappropriate) to 9 (highly appropriate). According to the RAND/UCLA manual, each survey item was classified as inappropriate, uncertain or appropriate based on the median panel rating and degree of panel disagreement (median 1-3.5 without disagreement = inappropriate; median 3.5-6.5 or any median with disagreement = uncertain; median 6.5-9 without disagreement = appropriate). As disagreement is not explicitly defined for 17 panellists in the RAND/UCLA manual, the disagreement threshold for 14-16 panellists was used. Disagreement was considered present when five or more panellists rated appropriateness in each extreme 3-point region (1-3 and 7-9). After analysis of the modified Delphi panel

approach, a digital meeting of all workshop participants took place on June 24th, 2020 to discuss the results of the Delphi round and, when not considered appropriate in terms of wording, to adapt the respective statements. For the rating of the modified versions of the items 2.2.1., 2.8.1, 5.2.1.1. and 5.2.1.2., a second digital voting was performed. The original versions of the online Delphi round are marked in italics. Missing ratings by pathologists are marked in the respective Tables. Median values and mean absolute deviation (MAD) of the ratings are shown.

Results

Standards for liver biopsy for patients with suspected autoimmune hepatitis (Supplementary Table 1)

Liver biopsy was considered mandatory for establishing the diagnosis of AIH, as clinical and laboratory features are neither sensitive nor specific enough to allow for a reliable diagnosis. The majority of participating pathologists (13/17) voted with the highest degree of consent on the applied rating scale (9 = highly appropriate) for liver biopsy being mandatory for the diagnosis of AIH. Meaningful evaluation of a liver biopsy requires a sufficiently large sample, preferably including at least 8 portal tracts. Therefore, length and diameter of the biopsy samples are important.[21,22] The histopathological report should provide information about the adequacy of the liver biopsy sample because the accuracy of histopathological interpretation relies on the amount and integrity of tissue available for assessment. The panel agreed that liver biopsies for the diagnosis of AIH should be obtained with a diameter corresponding to at least an 18G needle and preferably 16G or wider, and that the minimum length of the liver biopsy cylinder should be 1.5 cm, including at least 6-8 portal

tracts and optimally more than 10 portal tracts. It was also agreed that a connective tissue stain is mandatory during the histological diagnostic work-up of possible AIH, as the extent, distribution and maturity of fibrous tissue deposition are not only essential for determining the disease stage but also provide additional information helpful in dissecting differential diagnosis, such as drug- or toxin-induced liver damage. The presence of portal-based fibrosis provides evidence of underlying chronic liver damage, which may be helpful in the differential diagnosis of patients presenting with features of acute hepatitis (discussed further below). Viral hepatitis may mimic AIH, and reliable histological distinction between viral hepatitis and AIH is considered impossible. This applies to liver disease presenting either as acute or chronic. Autoimmune serological features such as raised levels of IgG and serum autoantibodies are quite frequently also observed in viral hepatitis. Thus, on their own they are insufficient for establishing the diagnosis of AIH. Therefore, testing for viral hepatitis, in particular for hepatitis A, B, C and E virus, as well as Epstein-Barr virus (EBV) and cytomegalovirus (CMV) is considered mandatory in the work-up of patients undergoing liver biopsy for evaluating the cause of hepatitis. While occasionally chronic viral hepatitis and AIH may co-exist, in the vast majority of cases only one aetiology exists or is clinically relevant.

Histological characteristics of autoimmune hepatitis (Table 1)

The panel strongly agreed that there are no pathognomonic histological characteristics of AIH (Table 1). A typical finding is a lymphoplasmacytic infiltrate which can include plasma cell clusters (defined as foci of ≥ 5 plasma cells; Fig.2A). Emperipolesis (presence of an intact lymphocyte within the cytoplasm of a hepatocyte; Fig.2B) and hepatocellular rosettes (small group of hepatocytes arranged

around a small, occasionally visible, central lumen; Fig.2C) were previously regarded as typical histological features of AIH but were not considered as being diagnostic of AIH in this Delphi round process. Both are considered as non-specific markers of inflammation severity and regeneration[17-19]

AIH is a chronic liver disease and may remain unrecognized for a long period of time, even in cases with an acute severe presentation. The general chronic course of AIH is reflected biochemically by long-term elevation of liver enzymes and/or histologically by the development of fibrosis. Therefore, the information about clinical or biochemical signs of chronic liver disease is highly desirable for a pathologist when evaluating a liver biopsy for suspected AIH. This information is thus considered critical for the pathologist and should be always provided together with the liver biopsy. Similarly, histological signs of chronicity are a valuable information for the clinician, and therefore the histopathological report should include a comment on the presence, maturity and extent of fibrosis. Furthermore, the dominant topography of inflammatory infiltrates should be reported, with a predominantly portal infiltrate characteristically occurring in cases with a chronic presentation and a predominantly lobular infiltrate being more typically seen in cases with an acute presentation.

Terminology used for the histological likelihood of autoimmune hepatitis (Table 2)

To provide information of the likelihood of AIH based on the histological findings, a standardized terminology was agreed by the panel to categorize the lowest, medium and highest likelihood of an AIH diagnosis in a given case as unlikely, possible and likely AIH respectively.

Criteria for the diagnosis of autoimmune hepatitis in the setting of portal and lobular hepatitis (Tables 3 and 4; the criteria are summarized in Table 5 and illustrated in Figures 1-2)

In the settings of chronic and acute presentations of AIH, which are usually (but not always) characterised by a dominant portal or lobular inflammatory infiltrate, respectively, the following criteria were agreed upon to define the likelihood of AIH as **unlikely**, **possible** or **likely**.

Portal hepatitis pattern (Table 3; the criteria are summarized in Table 5 and illustrated in Figures 1-2)

A liver biopsy with the histological pattern of portal hepatitis (Fig.2D-I) should be classified as **likely AIH**, if there is a portal lymphoplasmacytic infiltrate with at least one of the two following features: (i) more than mild interface hepatitis or (ii) more than mild lobular hepatitis, in the absence of histological features suggestive of another liver disease. The definition of mild inflammatory activity in AIH is given in Table 6. A liver biopsy with the histological pattern of portal hepatitis should be classified as **possible AIH**, if (i) the two likely features are lacking in the absence of histological features suggestive of another disease or (ii) or one or both of the two 'likely features are present in combination with histological features suggestive of another liver disease. A liver biopsy with the histological pattern of portal hepatitis should be classified as **unlikely AIH** if there are histological features suggestive of another liver disease and if 'likely features' of AIH are absent.

Lobular hepatitis pattern (Table 4; the criteria are summarized in Table 5 and illustrated in Figures 1-2)

A liver biopsy with the histological pattern of lobular hepatitis (Fig. 2J-M) should be classified as **likely AIH**, if it shows more than mild lobular hepatitis with or without centrilobular necroinflammation and at least one of the three following features: (i) lymphoplasmacytic infiltrates, (ii) interface hepatitis and (iii) portal-based fibrosis, in the absence of histological features suggestive of another liver disease. The histological pattern of lobular hepatitis should be classified as **possible AIH**, if it shows lobular hepatitis with or without centrilobular necroinflammation without any of the three 'likely features' of AIH, in the absence of histological features suggestive of another liver disease or if it shows any of the 'likely features' in combination with histological features suggestive of another liver disease. A liver biopsy with the histological pattern of lobular hepatitis should be classified as **unlikely AIH**, if there are histological features suggestive of another liver disease and if 'likely features' of AIH are absent.

Table 5 summarizes the criteria for likely, possible and unlikely AIH in both settings of portal and lobular hepatitis. Figure 2 summarizes schematically the criteria to define the likelihood of AIH as likely, possible or unlikely for both settings of dominant portal or lobular inflammatory infiltrates.

Grading of inflammatory activity in autoimmune hepatitis (Table 6)

It was agreed that the semi-quantitative assessment of the severity of inflammatory activity of AIH should be based on the Ishak's modified Histological Activity Index (mHAI).[23] The categories A (periportal or periseptal interface hepatitis), B (confluent necrosis) and C (focal/spotty lytic necrosis, apoptosis, and focal inflammation) were thought to be relevant for predicting the development of fibrosis and should therefore be applied. The category D of the mHAI (portal inflammation) was thought not to have predictive value and was thus not recommended for inclusion in grading disease activity of AIH. Mild inflammatory activity was defined as category A of the mHAI $\leq$1, category B =0 and category C $\leq$2. More than mild inflammation is thus defined as category A $\geq$2, category B $\geq$1 and category C $\geq$3.

Discussion

Liver biopsy is necessary for the diagnosis of AIH and establishing the diagnosis of AIH without histology should be an exception and limited to special clinical situations.[4,7-9,24] Such a scenario could be an elderly patient showing typical biochemical and serological signs of AIH, such as elevated IgG and the presence of specific serum autoantibodies such as anti-soluble liver antigen/liver pancreas antigen antibodies (anti-SLA/LP), who has an increased risk of bleeding after liver biopsy – if this patient has no history of new drug intake and viral hepatitis has been excluded thoroughly, a liver biopsy can be spared. We believe that the small risk for the patient attributable to the procedure of liver biopsy is justified as inappropriate treatment carries significantly greater risks. These concerns apply both to the failure to initiate immunosuppression in a patient who has AIH and in potentially giving long term immunosuppressive therapy to an individual not suffering from AIH. In addition to providing crucial information for establishing the diagnosis, liver biopsy also provides

important information about disease severity, which helps to guide decisions about immunosuppressive therapy. Finally, hepatic comorbidities such as fatty liver disease can be present in up to 15-30% of AIH patients and can best be detected by liver biopsy.[25] In this clinical setting, liver biopsy is helpful in assessing the importance of liver damage due to each component.

Whilst liver biopsy is widely accepted to be important for the diagnosis of AIH, it is also recognised that the diagnosis of AIH cannot be made on the basis of histological findings alone. Indeed, there is no single diagnostic test that can make the diagnosis, possibly with the exception of high titre anti-SLA/LP antibodies.[26] Therefore, liver biopsy interpretation requires clinical correlation and communication between hepatologists and pathologists. This particularly applies to cases where there are atypical clinical and/or histological findings. Important aspects that are helpful to make the correct diagnosis are the assessment of raised gammaglobulins, in particular a selective elevation of IgG, the exclusion of viral hepatitis, in particular by PCR in the setting of acute hepatitis, the drug history of the last 6 months and a history of previous elevated liver enzymes, supporting the chronic and / or relapsing course characteristic for AIH. This valuable information needs to be shared with pathologists and difficult cases should be discussed together between clinicians and pathologists.

Certain standards of liver biopsy should be maintained in order to support the quality of the histological report and the accuracy of diagnosis. Liver biopsies should have a minimum length of 1.5 cm, although longer biopsies (> 2.5 cm) clearly have further benefits, particularly for assessing the severity of fibrosis.[21,22] Since manifestation of AIH can be irregularly distributed in the liver, longer (and

even several) biopsies lower the risk of sampling error, especially in the grading and staging of the disease.[27] Even more important seems to be the diameter of a liver biopsy which is more relevant for the number of complete portal tracts than the length.[28]

Besides detailing the adequacy of a given biopsy specimen for diagnostic evaluation, the pathology report should also provide a systematic evaluation of all histological landmarks of the liver lobule (e.g. portal tracts, parenchyma, sinusoids, central veins) and include a comment on the presence and severity of fibrosis as a manifestation of chronic liver injury. In the context of an acute presentation and histological features of predominantly lobular hepatitis, the presence and quality of established fibrosis may favour a diagnosis of AIH over other causes of acute hepatitis (e.g. virus, drugs), which are less likely to have underlying fibrosis.[29] An assessment should be made of the maturity of fibrosis, in order to differentiate between mature fibrosis in the setting of chronic AIH and recent parenchymal collapse in the setting of severe acute hepatitis of any aetiology. A range of connective tissue stains for collagen, such as van Gieson, Masson trichrome or Sirius red and elastic fibres such as orcein, Victoria Blue or Elastica van Gieson, can be helpful to distinguish recent collapse from longstanding fibrosis.[30] While it seems important to evaluate both collagen and elastic fibers in a given biopsy, currently no recommendation can be made for particular staining methods due to lack of comparative studies. Thus, the method of choice depends on the experience and routine protocols established in each center.

Several histological features have been described as characteristic of AIH, but none of them is pathognomonic.[31] The scoring systems proposed by the International AIH Group (IAIHG) for establishing the diagnosis of AIH incorporate hepatocellular rosettes and emperipolesis as typical features supporting a diagnosis of AIH. In the 1999 IAIHG publication, the presence of hepatocellular rosettes was a histological feature that contributed to the diagnostic score for the likelihood of AIH.[3] The 2008 IAIHG simplified scoring system for AIH categorizes liver histology as typical for AIH when interface hepatitis, rosettes and emperipolesis are all present.[6] However, more recent studies have suggested that both of these features rather reflect liver cell injury and regeneration in the context of severe liver cell damage and that they lack diagnostic specificity for AIH.[17-19,32] Thus, these features cannot be considered as being diagnostic of AIH. Although emperipolesis and liver cell rosettes are not diagnostic features of AIH, they can be reported in the pathology report as a surrogate markers of disease severity. A lymphoplasmacytic infiltrate, including plasma cell clusters, and the inflammatory pattern of interface hepatitis seem to be more specific for AIH. We believe that the presence of readily identifiable plasma cells with focal plasma cell clusters (defined as > 5 plasma cells in one focus) could be regarded as suggestive for a diagnosis of AIH. However, the description of a plasma cell cluster proposed by this Delphi round process should be considered more a proposal than a definition, since no study has yet evaluated the optimal diagnostic cut-off for the definition of a plasma cell cluster.

Centrilobular injury with prominent hepatocellular necrosis has recently been recognised as being part of the histological spectrum of AIH.[10-15,33] The term central perivenulitis has also been used to describe this pattern of liver injury. This histological feature has been

mostly associated with DILI in the past but can be regularly found in the setting of severe acute manifestation of AIH. From a clinical point of view, the differentiation of acute presentation of AIH and DILI is pivotal, since AIH deserves long-term immunosuppression and DILI does not. Therefore, the diagnostic criteria of this Delphi round support the suggestion that cases showing primarily lobular necrosis and inflammation on liver biopsy can be AIH. Due to the limited evidence available, it remains still controversial which histological criteria are most useful to differentiate between DILI and AIH in the context of an acute lobular hepatitis.[34] This issue will be addressed by this group in a subsequent study (see below). Furthermore, DILI is a very good example when a close dialogue between clinicians and pathologists, preferably reviewing the biopsy data and the clinical data together, can improve to make the correct diagnosis.

A number of the statements and recommendations made in this consensus statement could be regarded as contentious. As an example, we recommend use of the mHAI score to be applied for grading of AIH, but recognise that other scoring systems, such as Metavir, Scheuer, Desmet and Batts-Ludwig, have also been proposed for the semi-quantitative assessment of inflammatory activity in liver disease.[35,36] However, these scores were mainly designed for the evaluation of chronic viral hepatitis. In our view, the mHAI has advantages over other systems since it is more granular and also allows separate and detailed assessment of centrilobular necroinflammatory changes than other scoring systems and thus seems more appropriate for grading acute lobular damage. However, the mHAI (and other scores) has only been validated in the setting of chronic viral hepatitis. To test the performance of the mHAI score

in the setting of acute hepatitis, we have designed a study for the validation of all the statements of this consensus statement (see below).

Another area of uncertainty concerns variant syndromes of cholestatic autoimmune liver diseases, the so-called AIH/PBC and AIH/primary sclerosing cholangitis (PSC) “overlap-syndromes”, and concomitant non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH) in AIH patients. The majority of cases of so called “overlap syndromes” involving AIH with PBC or PSC are better regarded as variants of PBC or PSC (PBC/PSC with “hepatitic features” or PBC/PSC with “AIH-like features”). According to this consensus statement, if features of PBC, PSC or NAFLD are present, a liver biopsy can still be classified as possible AIH. However, if a biopsy from a person suspected to have AIH clinically has unusually prominent biliary features such as bile duct loss or marked changes of chronic cholestasis (e.g. periportal deposits of copper, copper associated protein or periportal keratin 7 positive cells with an intermediate hepatobiliary phenotype), this should prompt further investigations to exclude the possibility that PBC or PSC may be the main diagnosis. More detailed histological studies are needed to characterize these incompletely understood disease entities.

Similarly, features of NAFLD and NASH can coexist with features of AIH, and increasingly patients with both conditions are being observed. As missing the diagnosis of AIH with its major prognostic and therapeutic consequences could be detrimental to the patient, it is important to not miss features of possible AIH in a patient with NASH, and the clinician needs to be notified of this possibility. The predictive value of specific features in distinguishing co-morbidity from severe NASH as well as from AIH with just NAFLD, as well as

the validity of scoring for the degree of inflammation for NASH and AIH in case of co-morbidity is a topic for future research. Further future research areas for AIH histology are summarized in supplementary table 2.

A further study by the International Autoimmune Hepatitis Pathology Group is planned to validate the criteria proposed in this paper for the diagnosis of AIH. This study will include assessing the utility of the proposed criteria in the differential diagnosis of acute AIH from non-acetaminophen drug-induced liver injury and acute viral hepatitis A, B, C and E infection, as well as its utility in diagnosing cases with severe acute and chronic manifestations of AIH.

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Author names in bold designate shared co-first authorship.

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Table 1: Histological characteristics of autoimmune hepatitis

Item	R1	R2	R3	R4	R5	R6	R7	R8	R9	Median (MAD†)	Rating
2.1. There are no pathognomonic histological features of AIH.	0	0	0	0	0	0	2	1	14	**9 (0)**	**Appropriate**
2.2.1. Knowledge of the duration of the liver disease is mandatory before assessing a biopsy for AIH	*0*	*0*	*1*	*1*	*3*	*3*	*5*	*0*	*4*	***7 (2.97)***	***Appropriate***
2.2.2. Knowledge of the duration of the liver disease is desirable before assessing a biopsy for AIH. ‡	0	0	0	0	0	0	0	0	13	**9 (0)**	**Appropriate**
2.3. Emperipolesis should be discarded as a diagnostic feature for AIH because of limited specificity.	0	0	0	0	0	0	2	1	14	**9 (0)**	**Appropriate**
2.4. Rosettes should be discarded as a diagnostic feature for AIH because of limited specificity.	0	0	0	1	0	1	2	2	11	**9 (0)**	**Appropriate**

2.5. When evaluating a biopsy for AIH the dominant pattern of inflammation, i. e. portal (chronic) hepatitis and lobular (acute) hepatitis, should be assessed.	2	0	0	0	0	0	1	3	11	**9 (0)**	**Appropriate**
2.6. An inflammatory infiltrate is referred to as lymphoplasmacytic if it contains groups of plasma cells (including plasma cell clusters) in addition to lymphocytes.	1	0	0	0	0	0	3	3	10	**9 (0)**	**Appropriate**
2.7. A plasma cell cluster is defined as ≥ 5 plasma cells in one focus.	1	0	0	1	0	1	4	2	8	**8 (1.48)**	**Appropriate**
2.8.1. Pathologists should differentiate between acute and chronic presentation of AIH in their report.	*0*	*1*	*1*	*0*	*4*	*0*	*7*	*0*	*4*	***7 (2.97)***	***Appropriate***
2.8.2. The pathology report should include a comment on the presence and severity of fibrosis.**	0	0	0	0	0	0	0	0	13	**9 (0)**	**Appropriate**

†MAD, mean absolute deviation; ‡the ratings of 4 pathologists were not applicable; the numbers of votes for the different ratings of consent (from R1=highly inappropriate to R9= highly appropriate) are displayed.

Table 2: Terminology of histological likelihood of the diagnosis of AIH

Item	R1	R2	R3	R4	R5	R6	R7	R8	R9	Median (MAD†)	Rating
3.1. To define the likelihood of the diagnosis of AIH the following terminology should be applied to cases with the lowest likelihood											
3.1.1 Atypical.	10	3	3	0	0	0	1	0	0	**1 (0)**	**Inappropriate**
3.1.2. Unlikely.	0	0	0	0	2	1	2	1	11	**9 (0)**	**Appropriate**
3.1.3. Undiagnostic.	9	2	3	1	1	0	0	1	0	**1 (0)**	**Inappropriate**
3.2. To define the likelihood of the diagnosis of AIH the following terminology should be applied to cases with medium likelihood											
3.2.1. Compatible.	3	0	2	2	2	2	3	0	3	**5 (2.97)**	**Uncertain and Disagreement**
3.2.2. Possible.	2	0	1	0	0	1	3	1	9	**9 (0)**	**Appropriate**
3.3. To define the likelihood of the diagnosis of AIH the following terminology should be applied to cases with the highest likelihood.											
3.3.1. Typical.	5	0	2	1	1	2	3	1	2	**5 (2.97)**	**Uncertain and Disagreement**
3.3.2. Likely.	1	0	0	0	2	0	2	1	11	**9 (0)**	**Appropriate**
3.3.3. Diagnostic.	9	1	3	1	0	0	0	2	1	**1 (0)**	**Inappropriate**

†MAD, mean absolute deviation; the numbers of votes for the different ratings of consent (from R1=highly inappropriate to R9= highly appropriate) are displayed.

Table 3: Diagnostic criteria for autoimmune hepatitis in the setting of portal hepatitis

Item	R1	R2	R3	R4	R5	R6	R7	R8	R9	Median (MAD†)	Rating
4.1. A liver biopsy with the histological pattern of portal hepatitis should be classified as **likely AIH** if there is a portal lymphoplasmacytic infiltrate with at least one of the following a) more than mild interface hepatitis b) more than mild lobular hepatitis in the absence of features suggestive of another liver disease.	0	0	0	0	0	0	1	4	12	**9 (0)**	**Appropriate**
4.2. A liver biopsy with the histological pattern of portal hepatitis should be classified as **possible AIH**											
4.2.1. If the two likely features are lacking in the absence of features suggestive of another disease.	0	0	0	0	0	0	4	4	9	**9 (0)**	**Appropriate**
4.2.2. or one or both of the two 'likely features' are present in combination with features suggestive of another liver disease.	2	0	0	0	0	2	4	4	5	**8 (1.48)**	**Appropriate**
4.3. A liver biopsy with the histological pattern of portal hepatitis should be classified as **unlikely AIH**											
4.3.1. if there are features suggestive of another liver disease.	0	0	0	0	1	0	3	3	10	**9 (0)**	**Appropriate**
4.3.2. and if likely features of AIH are absent.‡	0	0	0	0	0	0	0	0	14	**9 (0)**	**Appropriate**

†MAD, mean absolute deviation; ‡the ratings of 3 pathologists were not applicable; the numbers of votes for the different ratings of consent (from R1=highly inappropriate to R9= highly appropriate) are displayed.

Table 4: Diagnostic criteria for autoimmune hepatitis in the setting of lobular hepatitis

Item	R1	R2	R3	R4	R5	R6	R7	R8	R9	Median (MAD†)	Rating
5.1. A liver biopsy with the histological pattern of lobular hepatitis should be classified as **likely AIH** if it shows more than mild lobular hepatitis with or without centrilobular necroinflammation and at least one of the following: a) lymphoplasmacytic infiltrates b) interface hepatitis c) portal-based fibrosis in the absence of features suggestive of another liver disease.	0	0	0	0	0	1	1	3	12	**9 (0)**	**Appropriate**
5.2.1. A liver biopsy with histological pattern of lobular hepatitis should be classified as possible AIH											
5.2.1.1. if there is lobular hepatitis and/or centrilobular necroinflammation‡	*0*	*0*	*0*	*0*	*1*	*1*	*1*	*4*	*9*	***9 (0)***	***Appropriate***
5.2.1.2. or (sub-)massive hepatic necrosis ‡	*0*	*0*	*0*	*0*	*1*	*2*	*2*	*2*	*9*	***9 (0)***	***Appropriate***
5.2.2. A liver biopsy with the histological pattern of lobular hepatitis should be classified as **possible AIH**											
5.2.2.1. if it shows lobular hepatitis with or without centrilobular necroinflammation without any of the likely features of AIH, in the absence of features suggestive of another liver disease§	0	0	0	0	0	0	0	0	14	**9 (0)**	**Appropriate**

5.2.2.2. or if it shows any of the 'likely features' in combination with features suggestive of another liver disease.¶	0	0	0	1	0	0	1	3	10	***9 (0)***	***Appropriate***
5.3. A liver biopsy with the histological pattern of lobular hepatitis should be classified as **unlikely AIH**											
5.3.1. if there are features suggestive of another liver disease	0	0	1	0	0	2	1	2	11	**9 (0)**	**Appropriate**
5.3.2. and if likely features of AIH are absent.¶	0	0	0	0	0	0	0	3	12	**9 (0)**	**Appropriate**

†MAD, mean absolute deviation; ‡the rating of 1 pathologist was not applicable; §the ratings of 3 pathologists were not applicable; ¶the ratings of 2 pathologists were not applicable; the numbers of votes for the different ratings of consent (from R1=highly inappropriate to R9= highly appropriate) are displayed.

Table 5: Diagnostic criteria for autoimmune hepatitis in the settings of both portal lobular hepatitis

	Portal hepatitis	Lobular hepatitis
Likely AIH	Portal lymphoplasmacytic infiltrate PLUS one or both of the following features 1. more than mild interface hepatitis 2. more than mild lobular inflammation - in absence of histological features suggestive of another liver disease	More than mild lobular hepatitis (+/- centrilobular necroinflammation) PLUS at least one of the following features 1. lymphoplasmacytic infiltrates 2. interface hepatitis 3. portal-based fibrosis - in absence of histological features suggestive of another liver disease
Possible AIH	Portal lymphoplasmacytic infiltrate - without either of the likely features 1 or 2 above - in absence of histological features suggestive of another liver disease OR - with one or both of likely features above - in presence of histological features suggestive of another liver disease	Any lobular hepatitis (+/- centrilobular necroinflammation) - without any of the likely features 1-3 above - in absence of histological features suggestive of another liver disease OR - with any of the likely features above - in presence of histological features suggestive of another liver disease
Unlikely AIH	Portal hepatitis - without either of the likely features above - in presence of histological features suggestive of another liver disease	Any lobular hepatitis - without any of the likely features above - in presence of histological features suggestive of another liver disease

Criteria for the diagnosis of likely, possible or unlikely AIH in the setting of portal or lobular hepatitis are shown.

Table 6: Grading of inflammatory activity in autoimmune hepatitis

Item	R1	R2	R3	R4	R5	R6	R7	R8	R9	Median (MAD†)	Rating
6.1. Grading of inflammatory activity of AIH											
6.1.1. should be based on the modified Ishak Score (mHAI)	0	0	0	0	0	0	4	2	11	**9 (0)**	**Appropriate**
6.1.2. and its categories A (periportal or periseptal interface hepatitis),	0	0	0	0	0	0	2	2	13	**9 (0)**	**Appropriate**
6.1.3. B (confluent necrosis)	0	0	0	0	0	0	3	1	13	**9 (0)**	**Appropriate**
6.1.4. and C (focal /spotty lytic necrosis, apoptosis, and focal inflammation)	0	0	0	0	0	0	2	1	14	**9 (0)**	**Appropriate**
6.1.5. Category D (portal inflammation) should not be included	0	1	1	0	0	0	2	1	12	**9 (0)**	**Appropriate**
6.2. Inflammatory activity should be referred to as 'mild' if											
6.2.1 Category A≤1‡	0	0	0	1	0	0	1	1	13	**9 (0)**	**Appropriate**
6.2.2. and category B=0‡	0	0	0	0	0	0	2	0	14	**9 (0)**	**Appropriate**
6.2.3 and category C≤2‡	0	0	0	0	0	0	1	0	15	**9 (0)**	**Appropriate**

†MAD, mean absolute deviation; ‡the rating of 1 pathologist was not applicable; the numbers of votes for the different ratings of consent (from R1=highly inappropriate to R9= highly appropriate) are displayed.

Figure legends

Figure 1: Histological features of AIH

(A) A typical histological finding in AIH is a lymphoplasmacytic inflammatory infiltrate including plasma cell clusters (arrows); **(B)** Emperipolesis (arrow), i.e. presence of an intact leucocyte within the cytoplasm of a hepatocyte, and **(C)** hepatocellular rosettes, i.e. a small group of hepatocytes arranged around a small, occasionally visible, central lumen (asterisk), are commonly seen in patients with AIH, but are not considered to be specific for the diagnosis of AIH**. Chronic presentation of AIH** is usually characterised by a dominant portal inflammatory infiltrate with interface activity of variable severity. **(D-G)** More than mild or **(H)** mild interface activity; **(I)** severe portal inflammation with mild interface activity. Acute presentation of AIH is usually characterised by a dominant lobular inflammatory infiltrate. **(J)** Moderate lobular hepatitis with a centrilobular pattern associated with centrilobular necrosis (central perivenulitis); **(K)** severe lobular hepatitis with confluent (arrow) and bridging (asterisk) necrosis**; (L, M)** Mild lobular hepatitis. Furthermore, typical features of AIH, such as centrilobular plasma cell clusters (**L**, arrow) and/or non-specific features, such as emperipolesis (**M**, arrows), can be present. (1A-C,G,M) Haematoxylin and eosin stain, (1A-C,G,M) x40 magnification, (1H,L) x20 magnification, (1D,E,F,I-K) x10 magnification.

Figure 2: Schematic summary of the criteria to define the likelihood of AIH

(A) The presence of a predominantly portal lymphoplasmacytic infiltrate with (a) more than mild interface hepatitis, or (b) more than mild lobular hepatitis, or (c) more than mild lobular and interface hepatitis, in the absence of histological features suggestive of another liver disease is LIKELY to be autoimmune hepatitis (solid arrows). In the presence of histological features suggestive of another liver disease,

a, b or c suggest POSSIBLE autoimmune hepatitis (solid arrows). A predominantly portal lymphoplasmacytic infiltrate without more than mild lobular or interface hepatitis (d), in the absence of histological features of another liver disease suggests POSSIBLE autoimmune hepatitis, but is UNLIKELY to be autoimmune hepatitis in the presence of another liver disease (dashed arrows). **(B)** The presence of a predominantly lobular hepatitis, more than mild in severity, with or without centrilobular necroinflammation and (a) lymphoplasmacytic infiltrates, or (b) interface hepatitis, or (c) portal fibrosis, in the absence of histological features suggestive of another liver disease, is LIKELY to be autoimmune hepatitis (solid arrows). In the presence of histological features suggestive of another liver disease, a, b or c suggest POSSIBLE autoimmune hepatitis (solid arrows). Lobular inflammation of any degree with or without centrilobular necroinflammation but without lymphoplasmacytic infiltrates, interface hepatitis or portal fibrosis (d), in the absence of histological features of another liver disease, suggests POSSIBLE autoimmune hepatitis, but is UNLIKELY to be autoimmune hepatitis in the presence of another liver disease (dashed arrows). Also see Table 5. Illustrations by Miss Rashmil Saxena, BFA.

Fig.1A

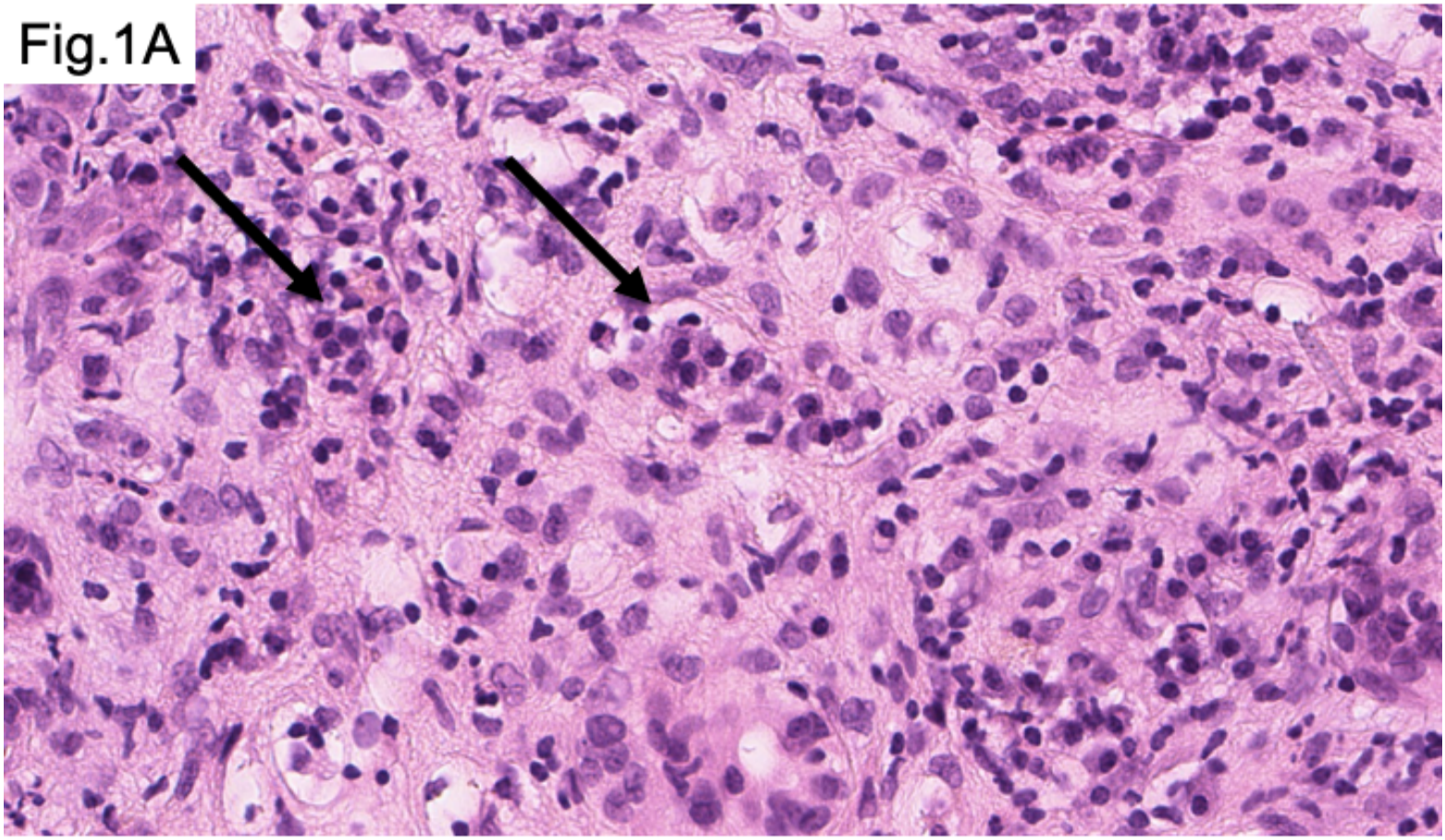

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Fig.1B

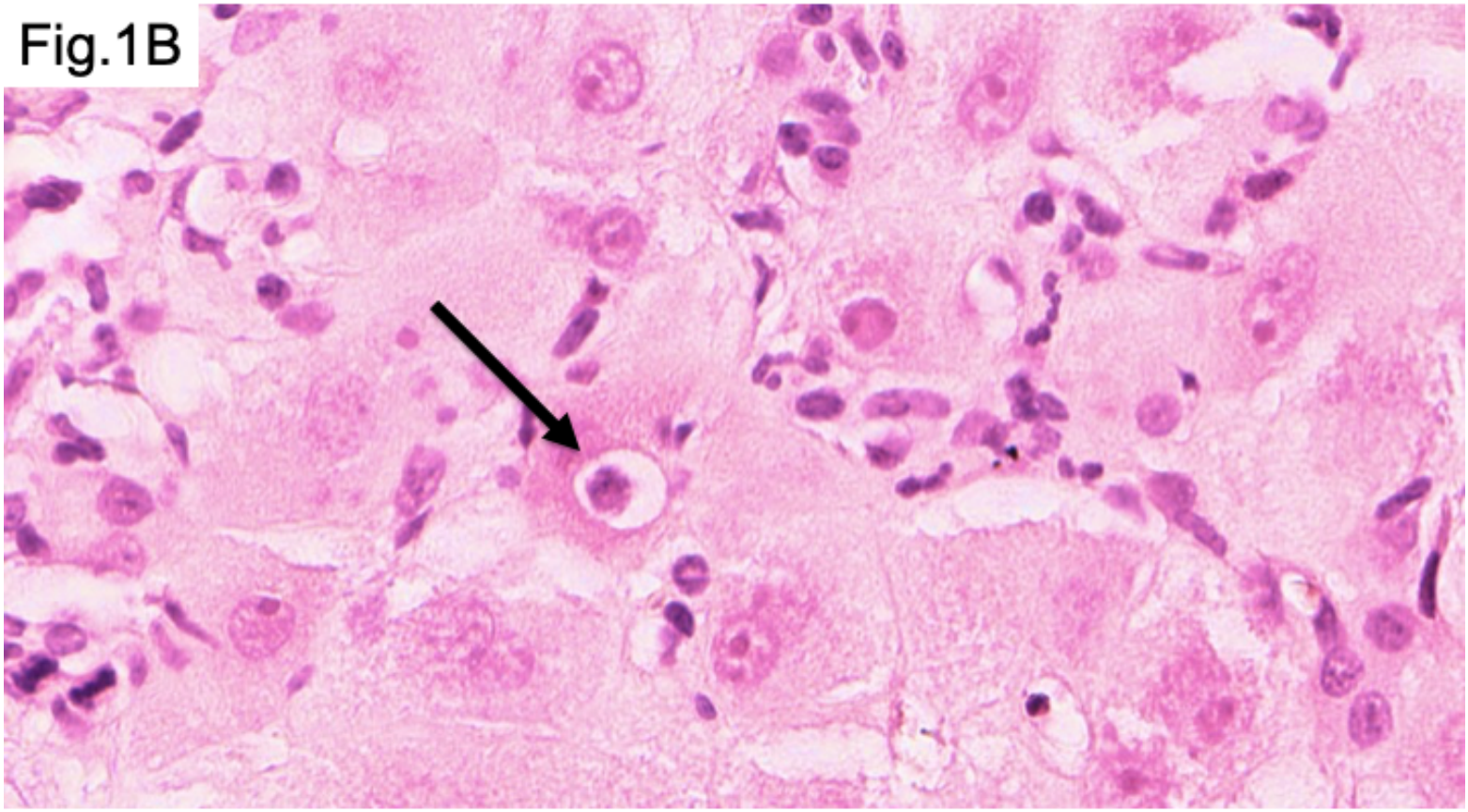

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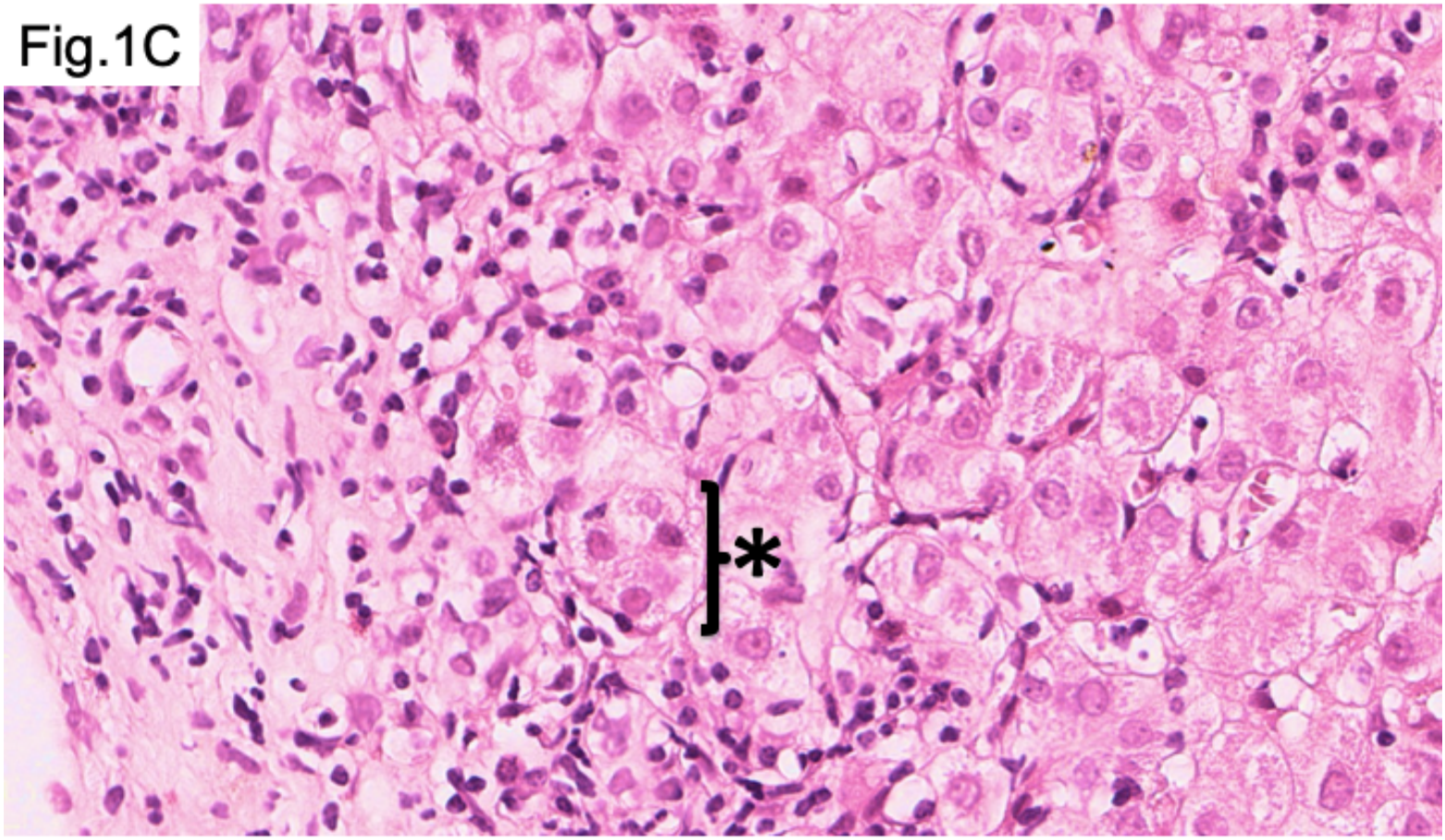
Fig.1C



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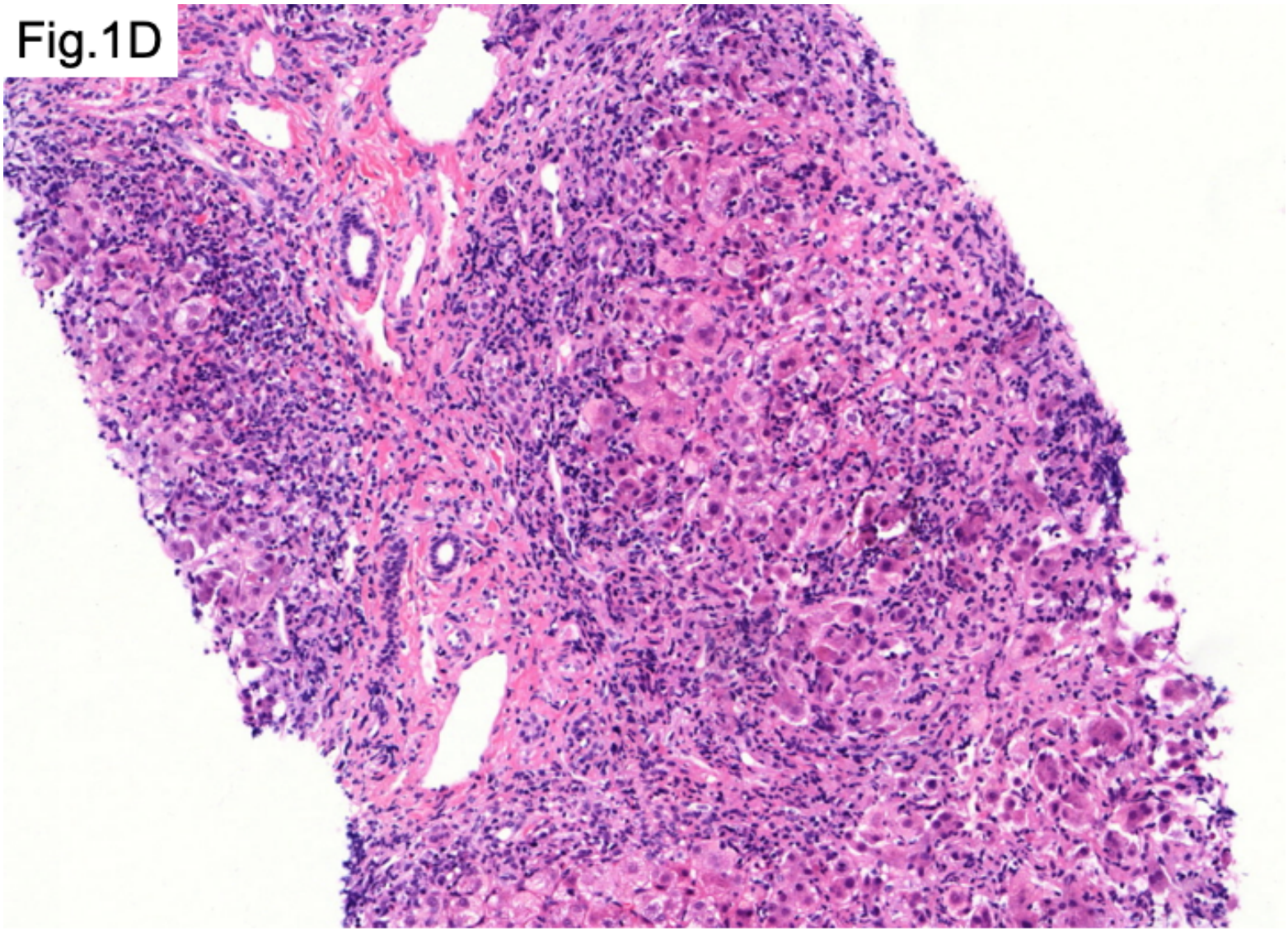

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Fig.1E

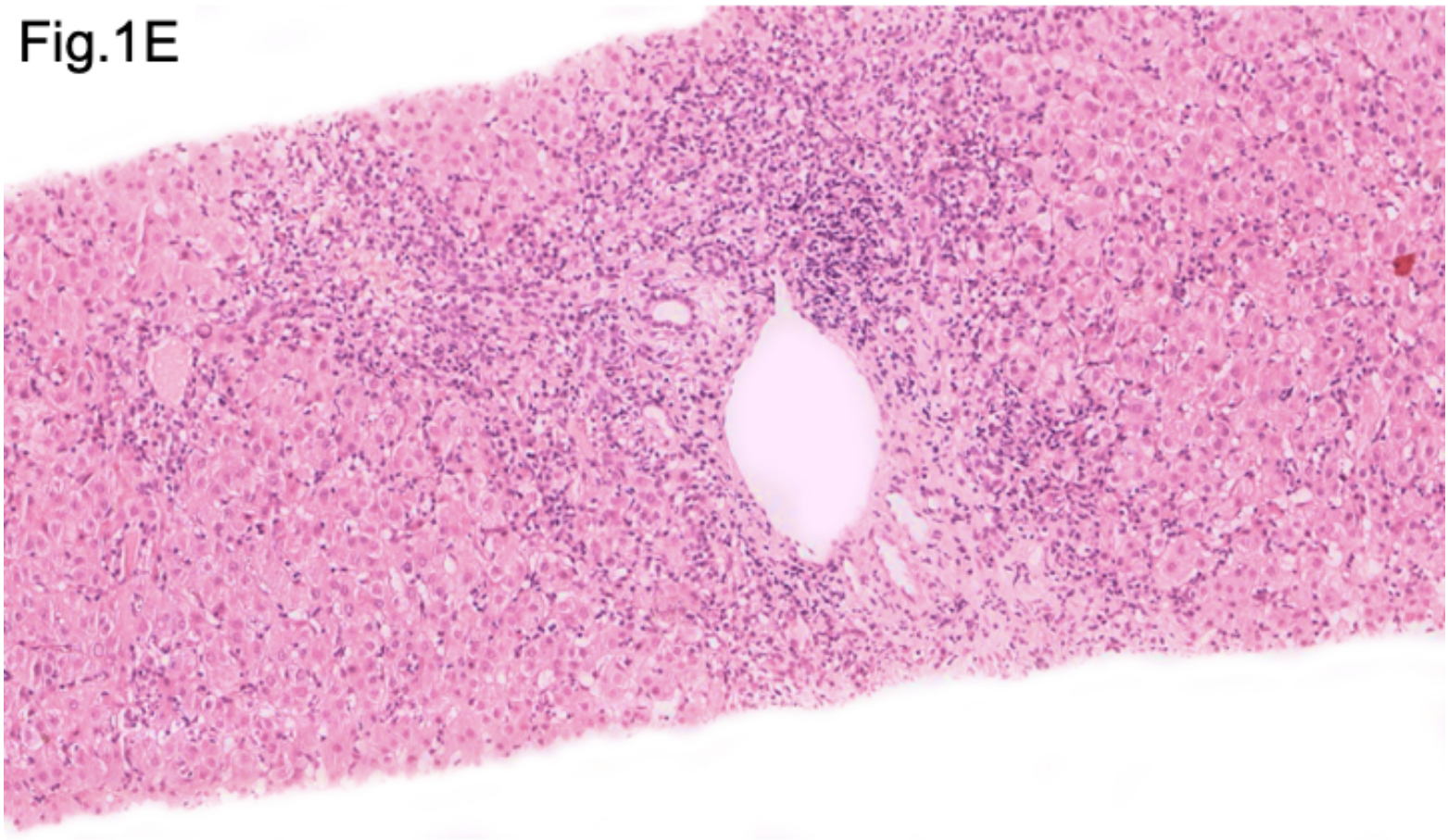

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Fig.1F

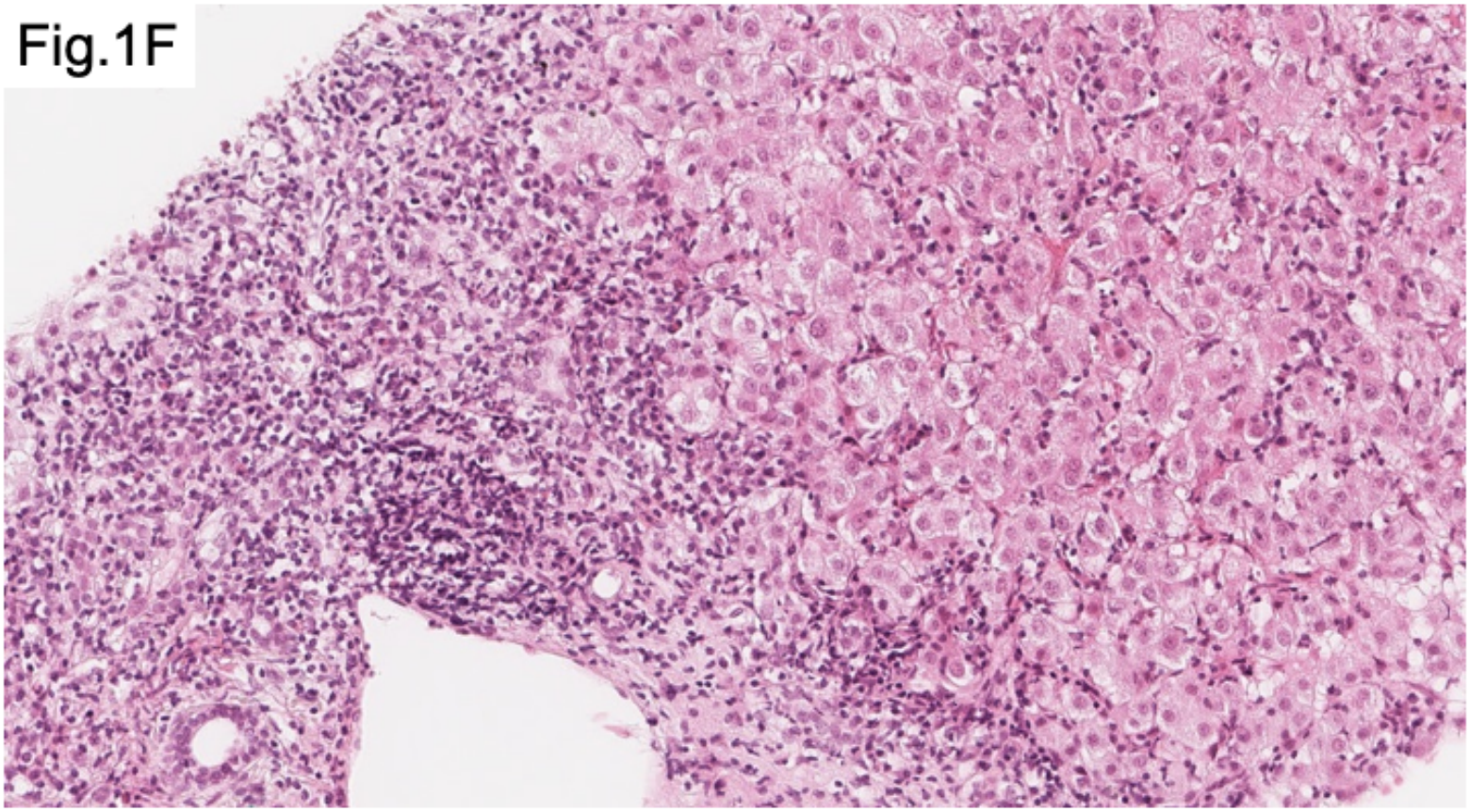

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Fig.1G

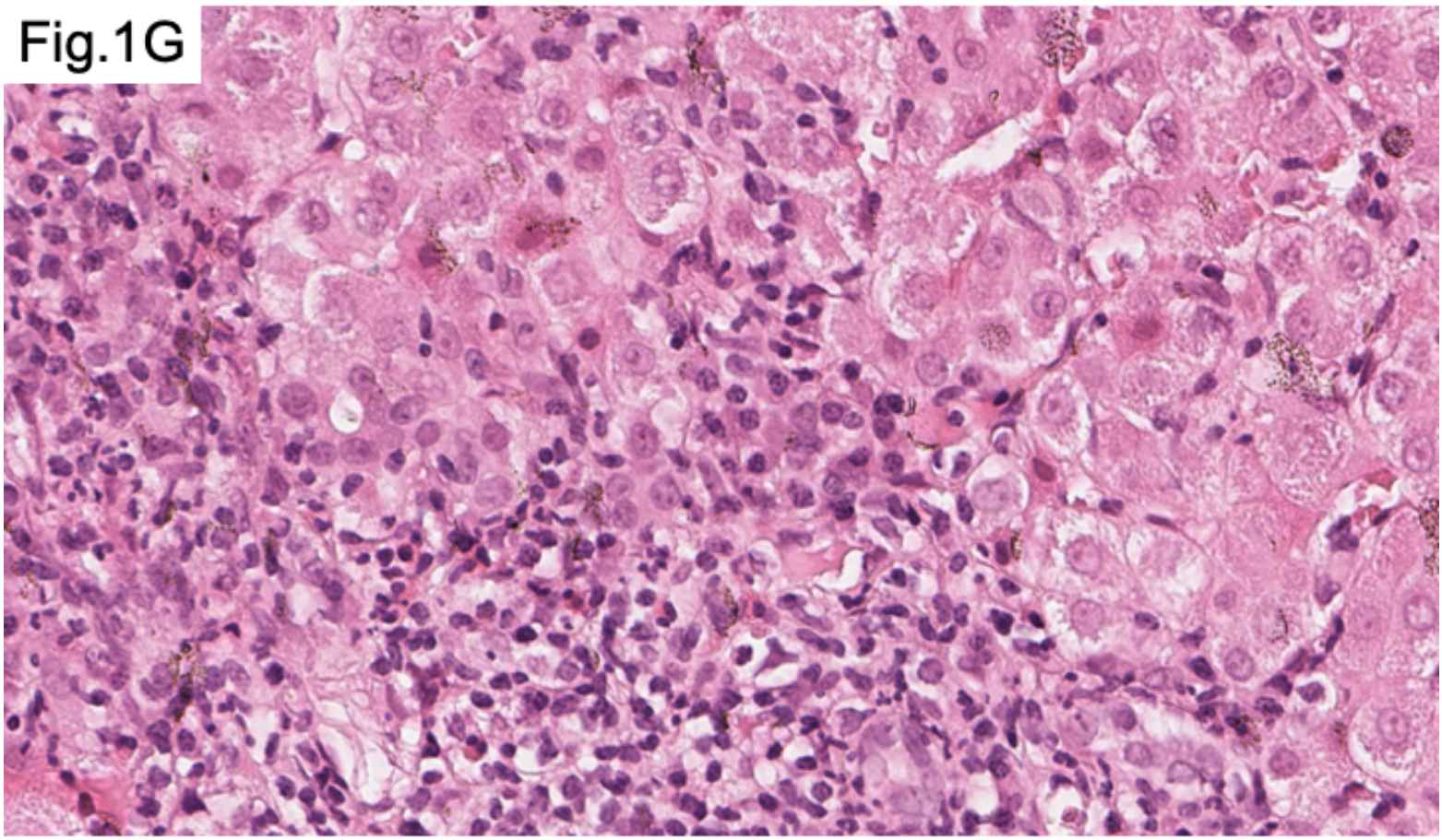

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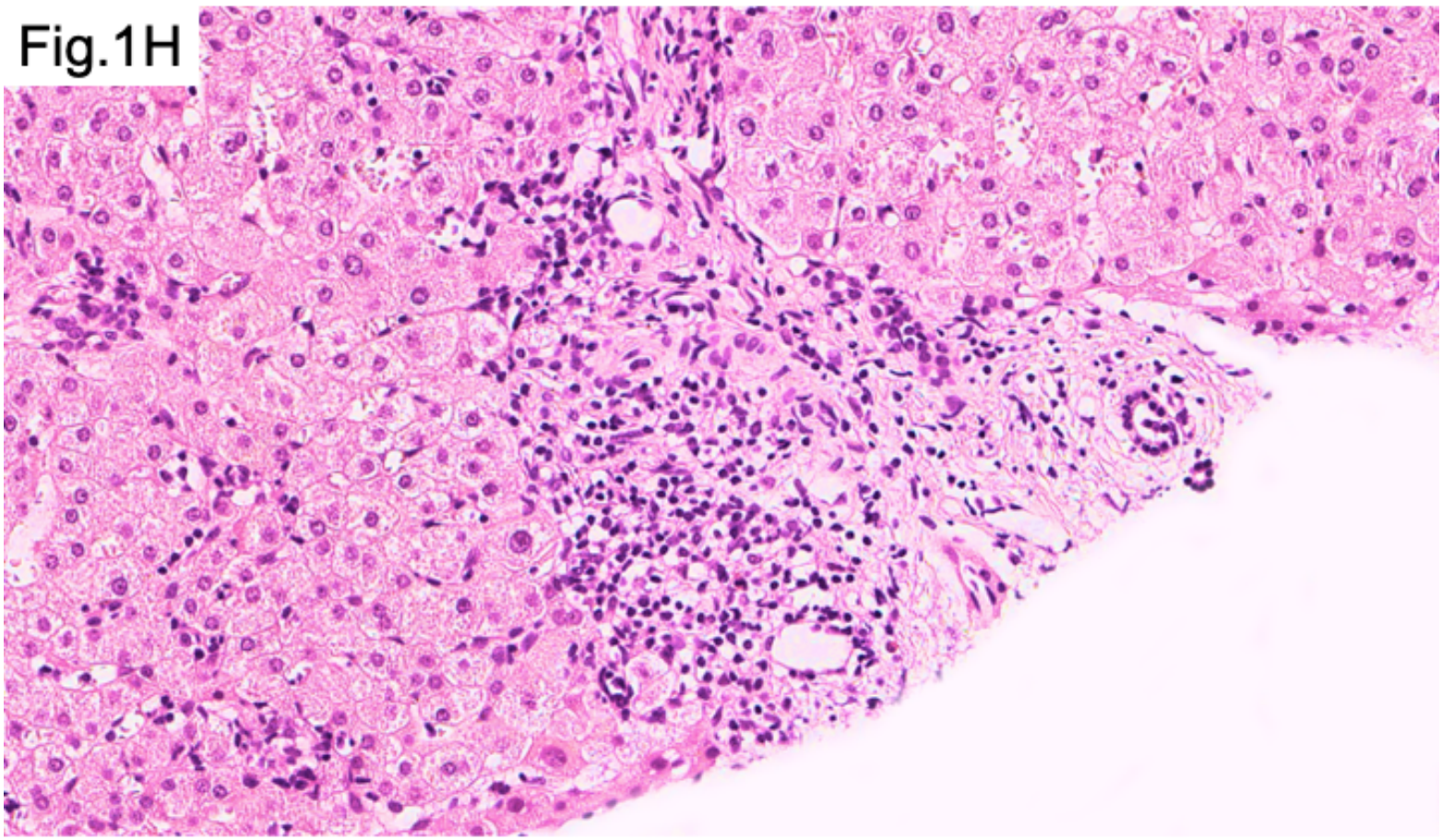
Fig.1H



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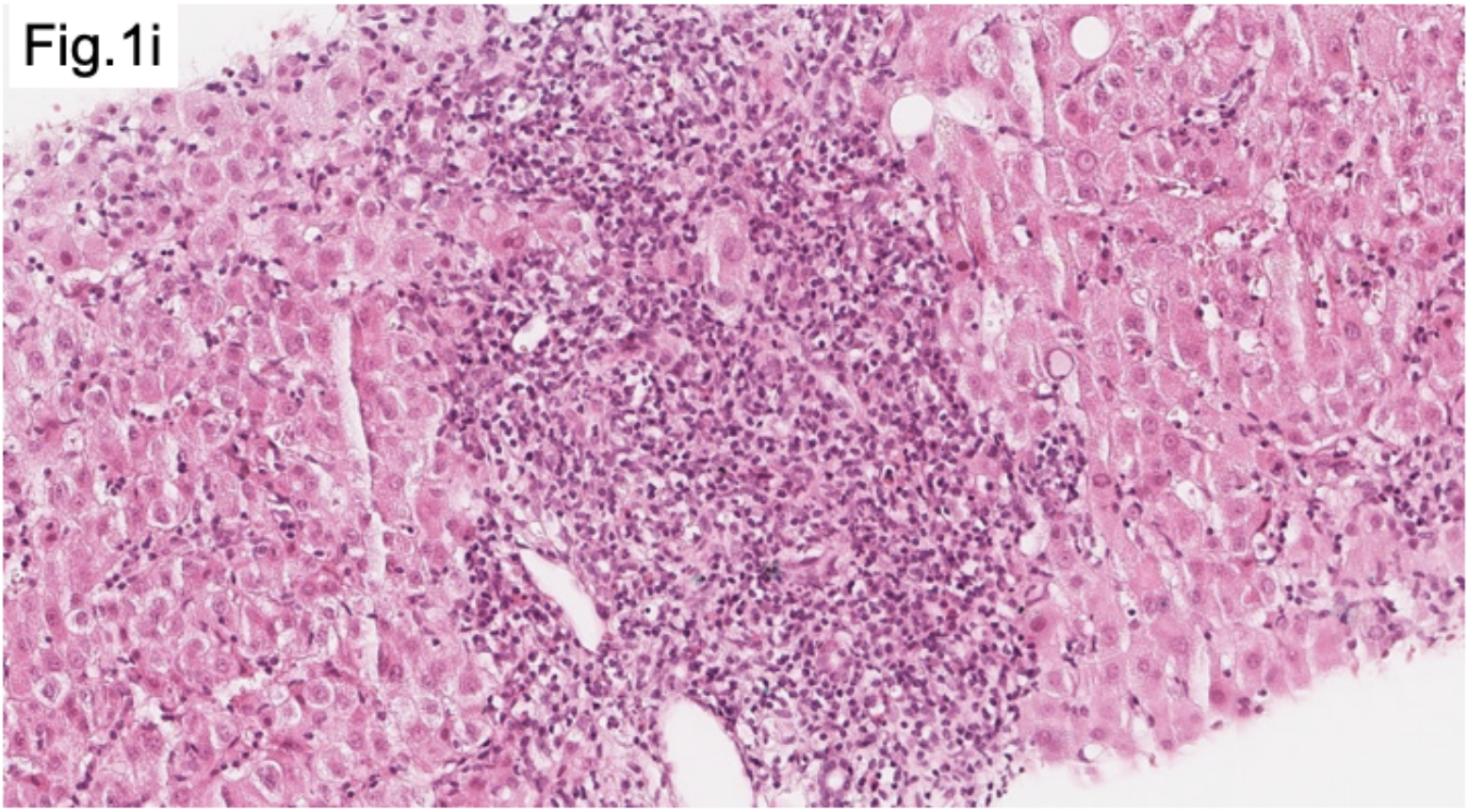

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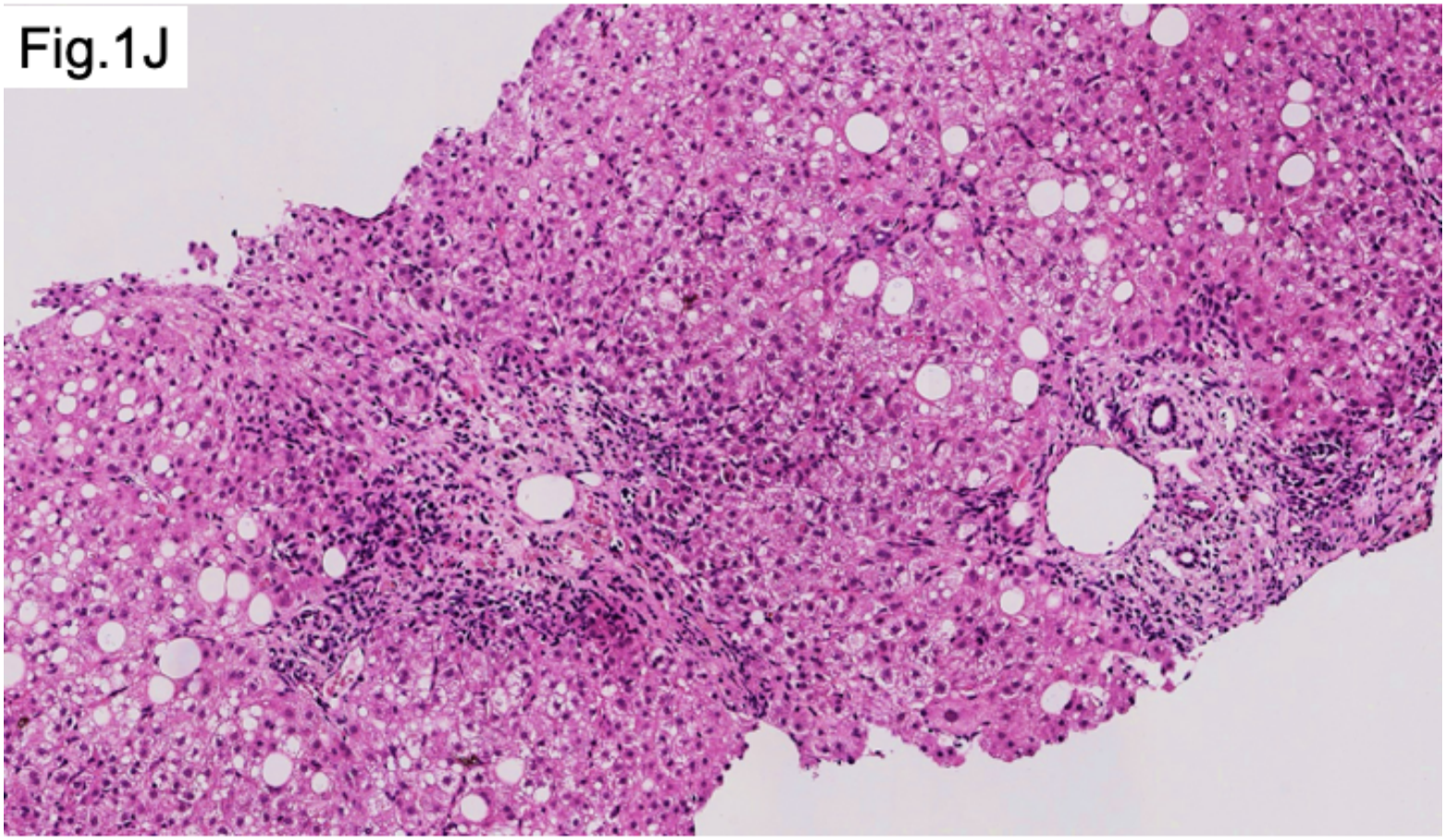

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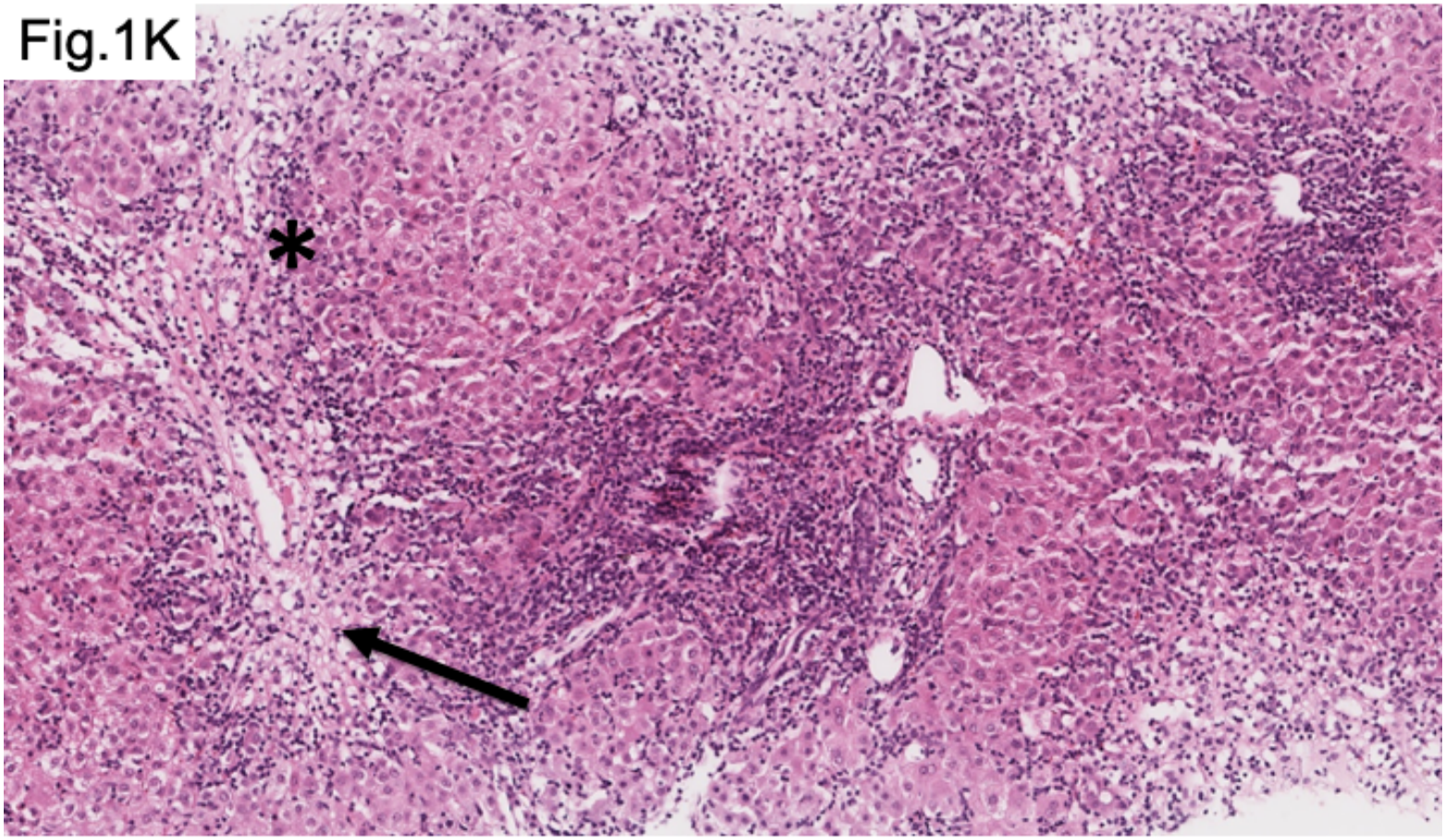
Fig.1K



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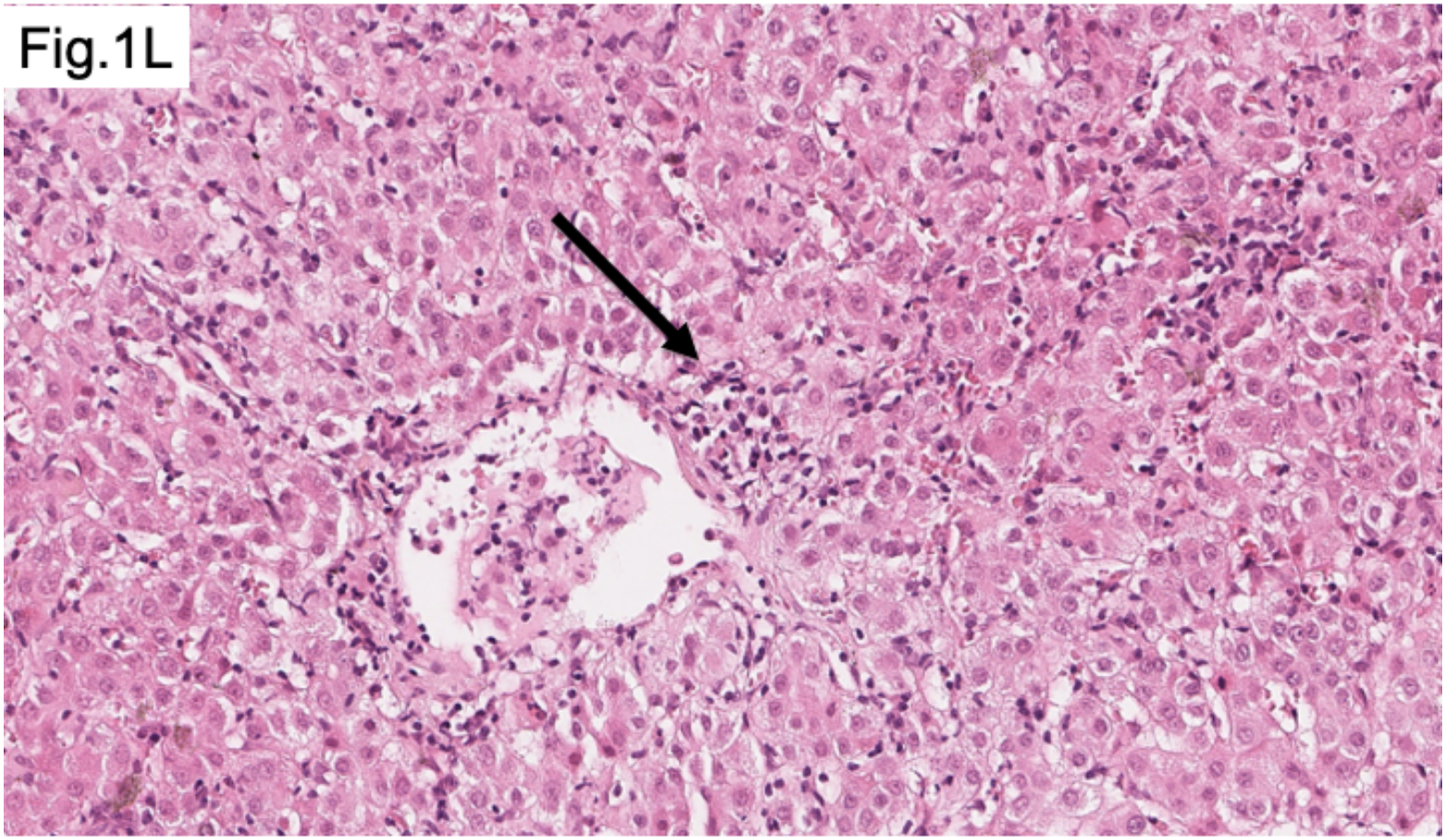

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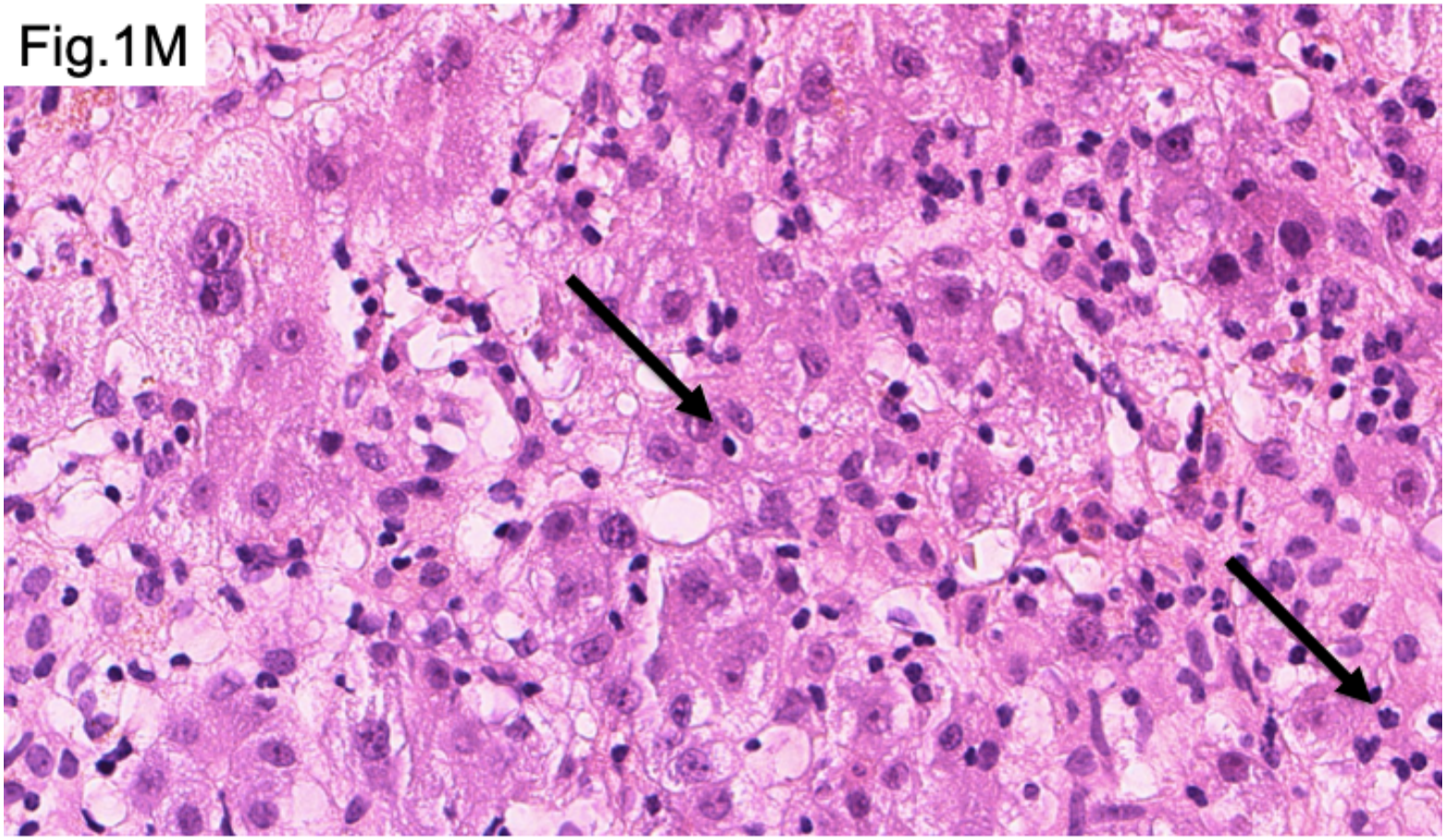
Fig.1M



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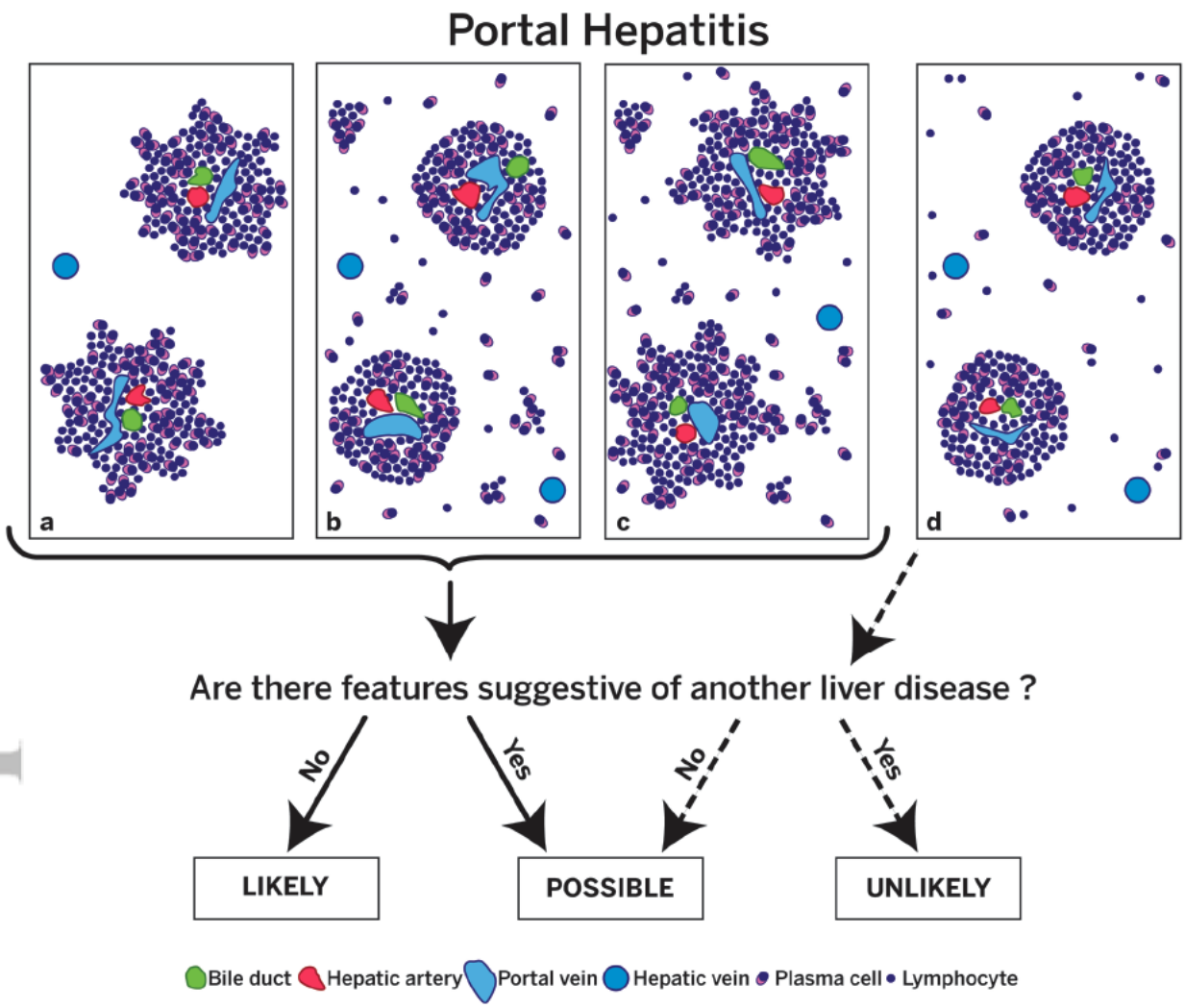

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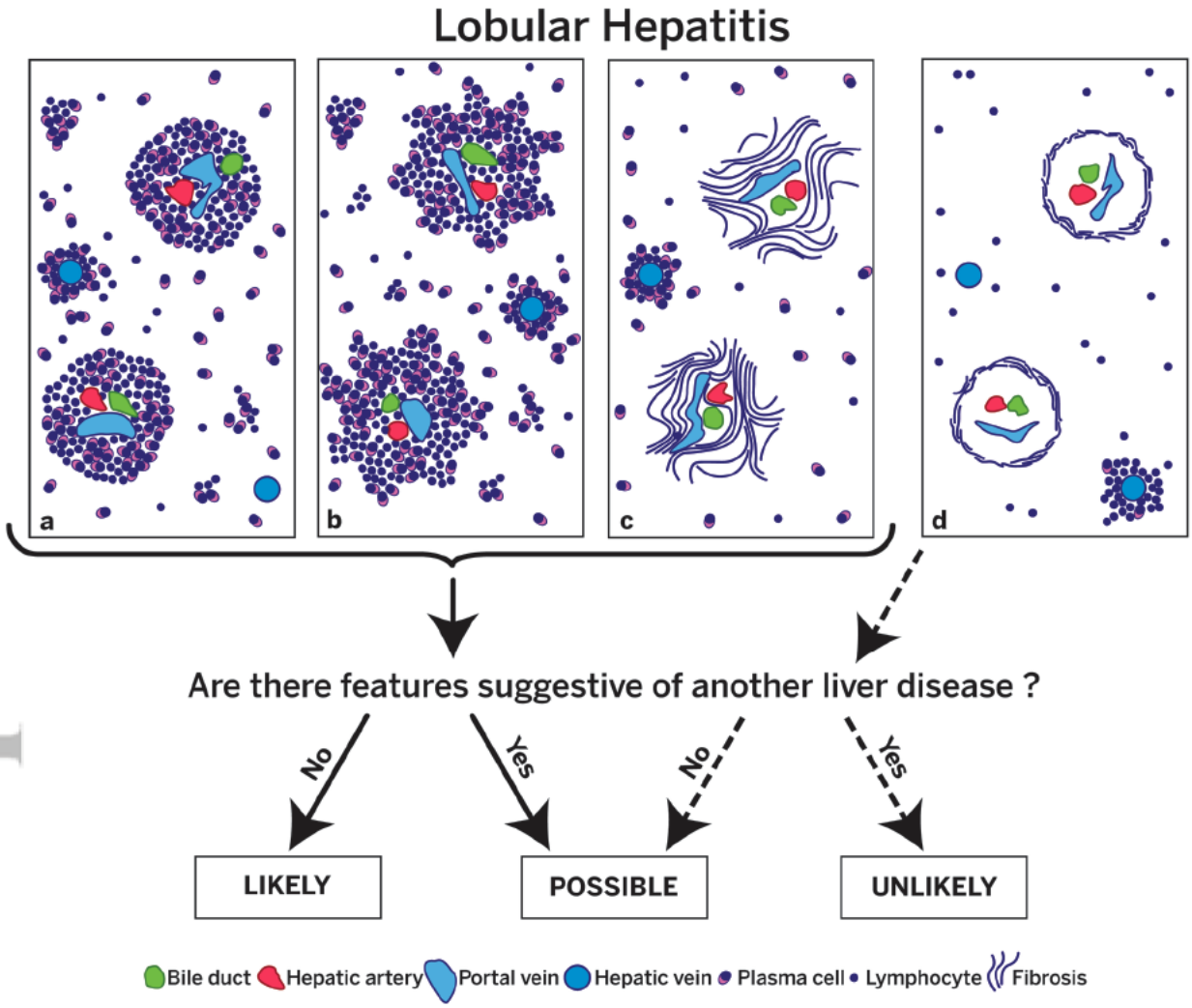

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