

Newcastle patient

Dr Yvonne Bury

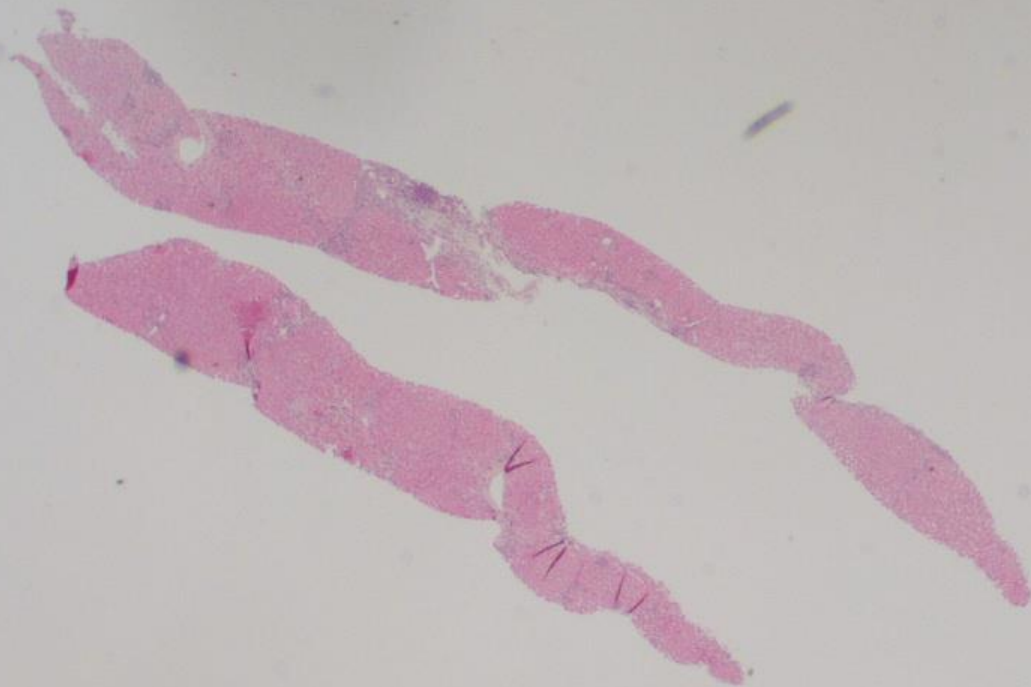
History

- Female 39 years old with PBC, AMA positive 1/640, M2 strongly positive
- Transplanted on 16/01/2017
- Explant: established biliary type cirrhosis with ductopenia in keeping with primary biliary cholangitis (PBC) with superadded bilirubinostasis compatible with decompensation
- Times 0 biopsy: moderate reperfusion injury and mild macrovesicular steatosis
- At the same time right oophorectomy: 150mm seromucinous cystadenoma with 80mm nodule of mature cystic teratoma in the wall, no evidence of malignancy.
- [At time of transplant: DR1 donor specific antibody 10-11,000 MFI]

- No immunosuppression pre-transplant
- Post-op (Jan 2017) was taking Tacrolimus 2mg BD, Azathioprine 75mg OD, Prednisolone 20mg then 15mg OD
- AMA continues to be strongly positive (>1/640)

1st biopsy Mon 27/03/2017 (day 70)

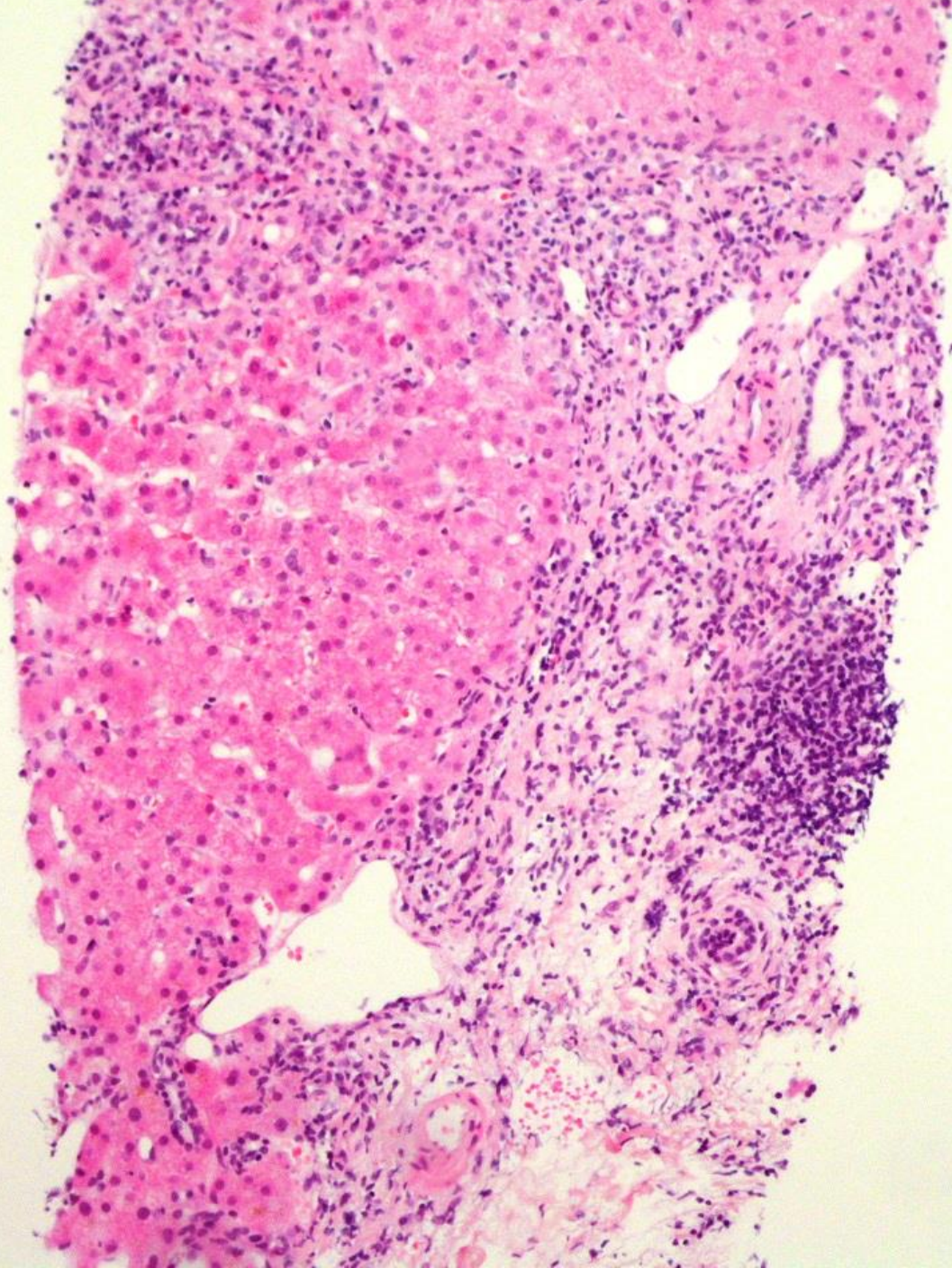
- Had been on Tacrolimus 2mg BD, Azathioprine 75mg and Prednisolone 20mg
- Clinical info:
 - ALT 27 increased to 556,
 - ALP 98 increased to 198
 - Tacrolimus level 4.2
 - Pulsed before 1x / 2x / after biopsy with Methylpred ***
 - US on 25th/ CT 26th no vascular abnormalities
 - Car accident few weeks ago since RUQ pain
 - CMV mismatch
- Further info: issues with steroid post transplant regime



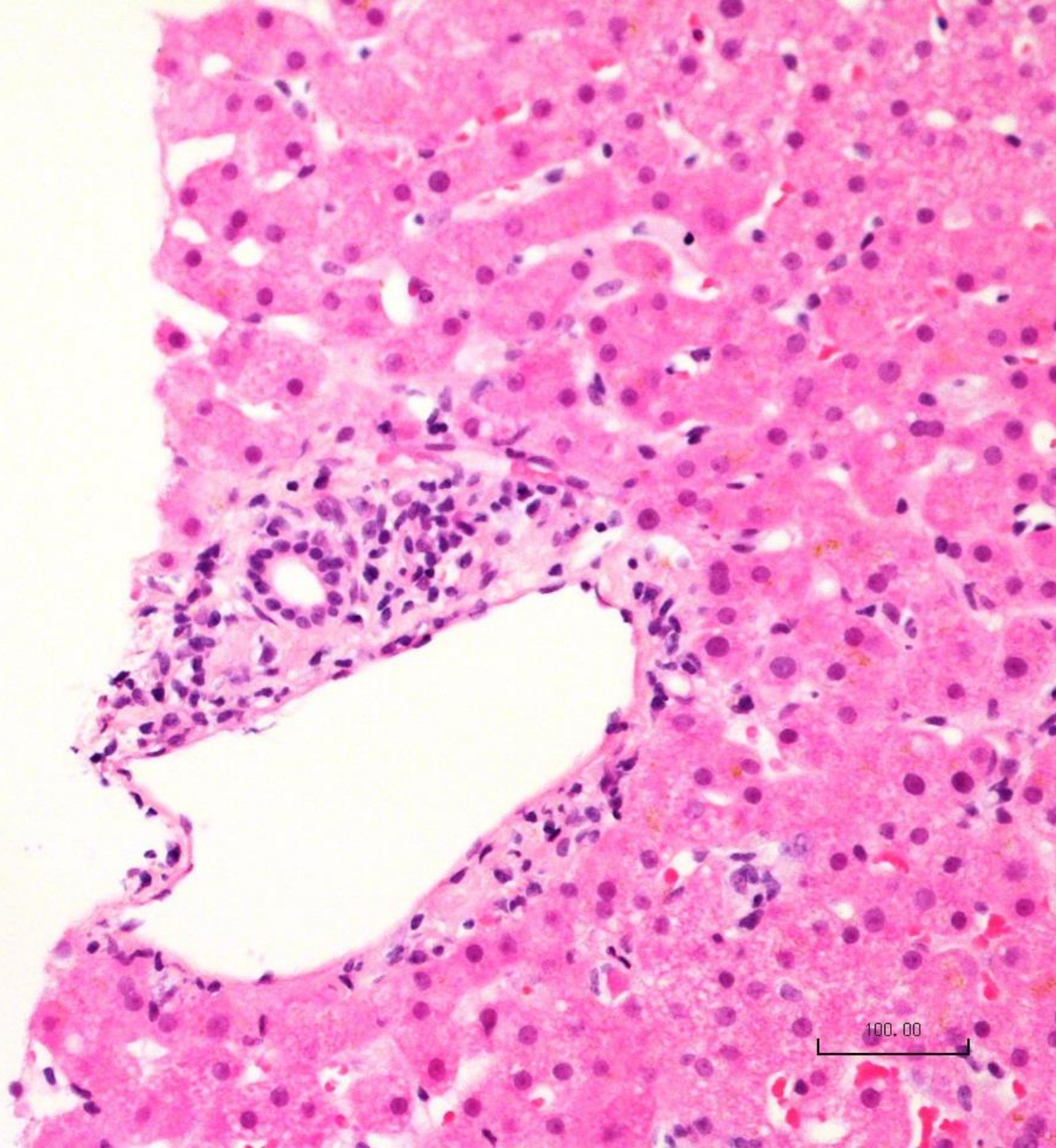
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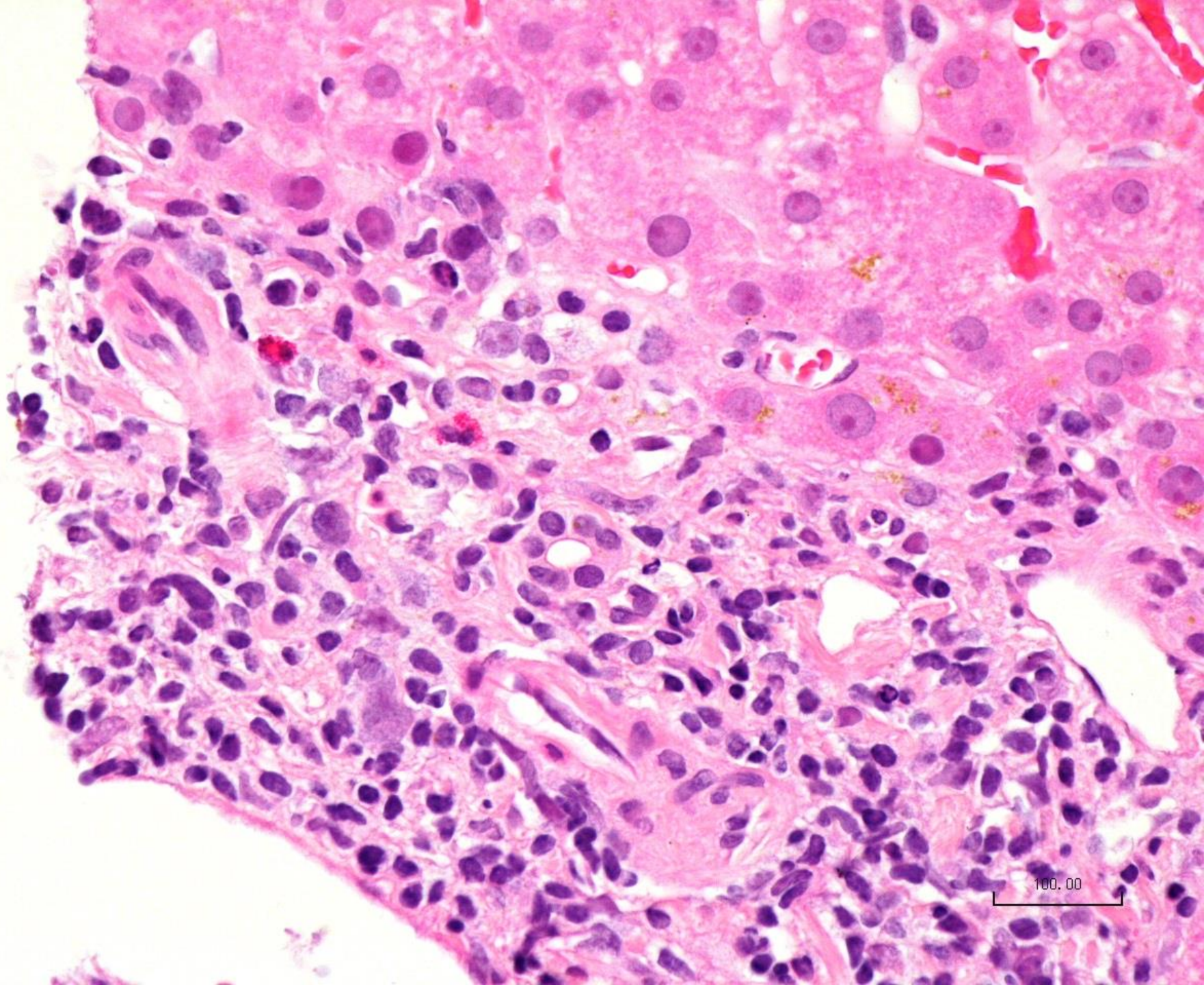


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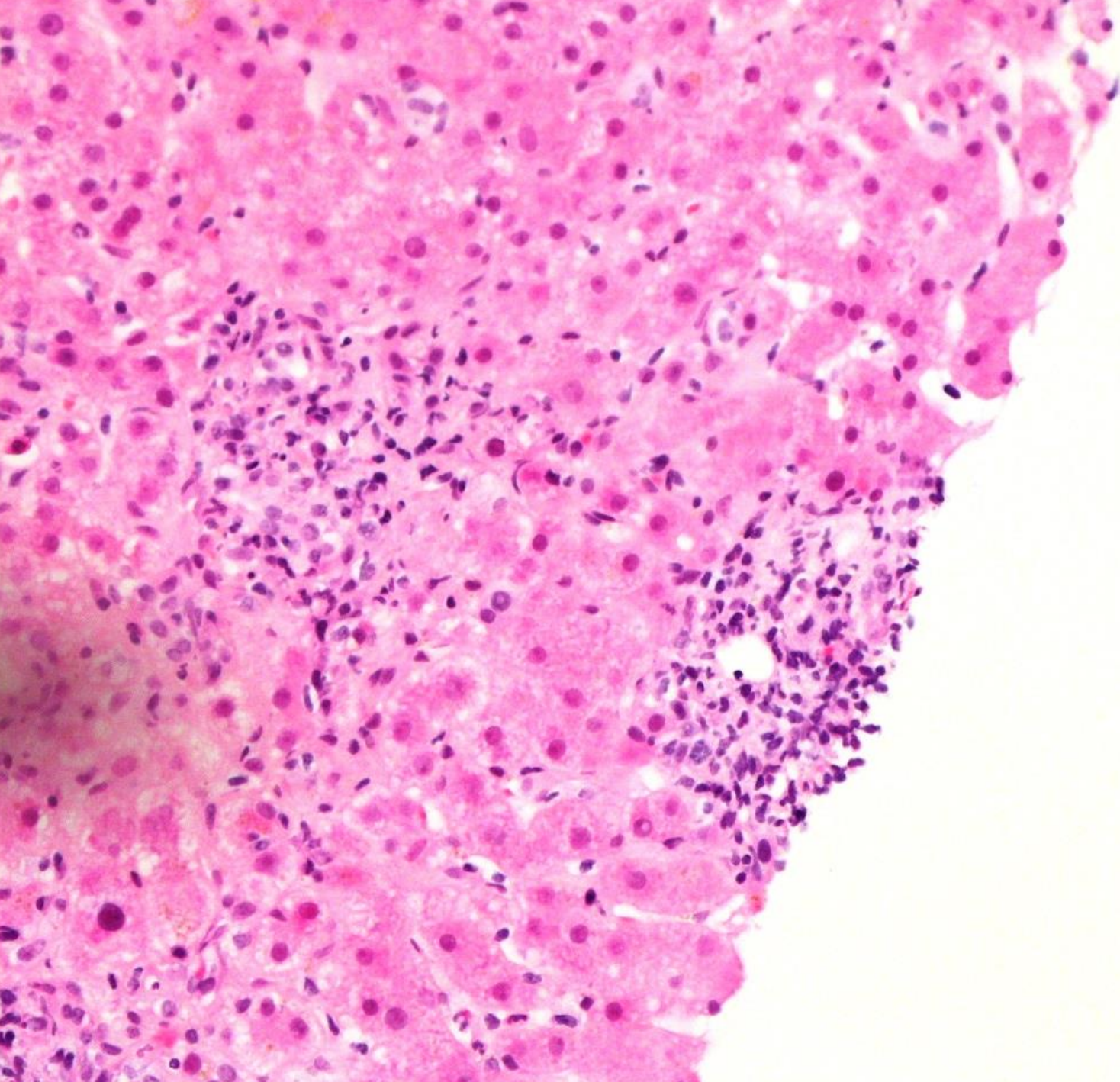


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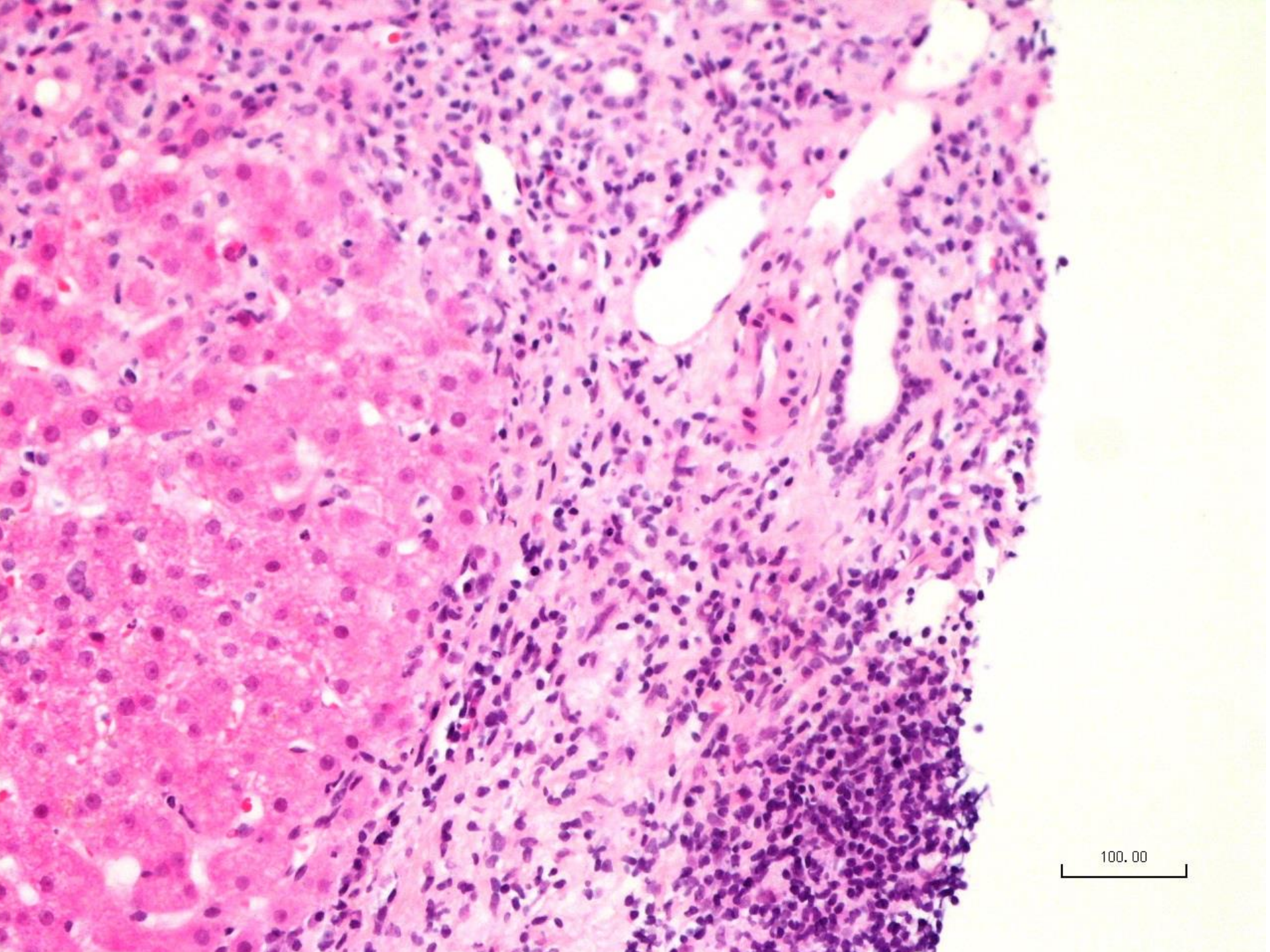




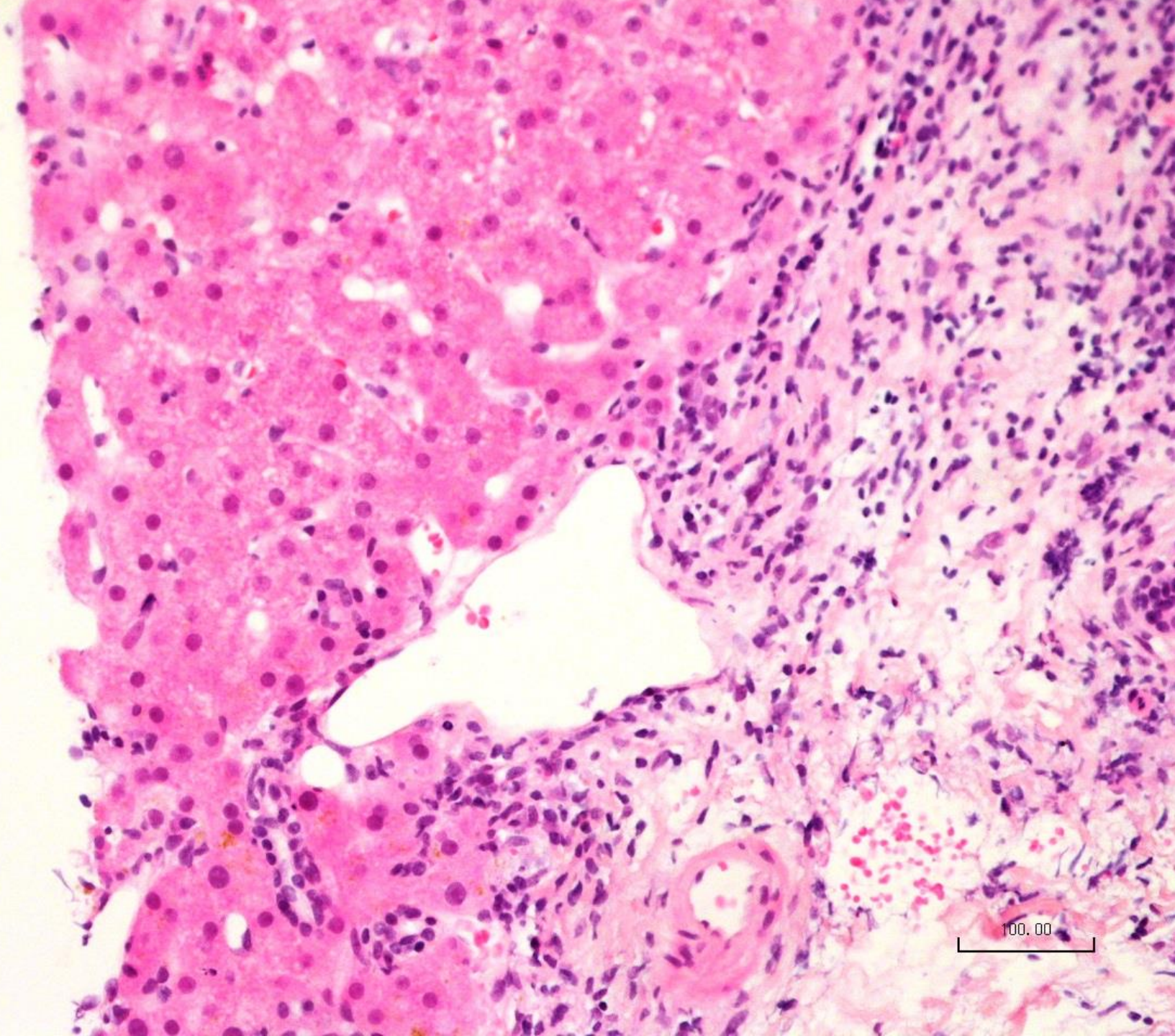
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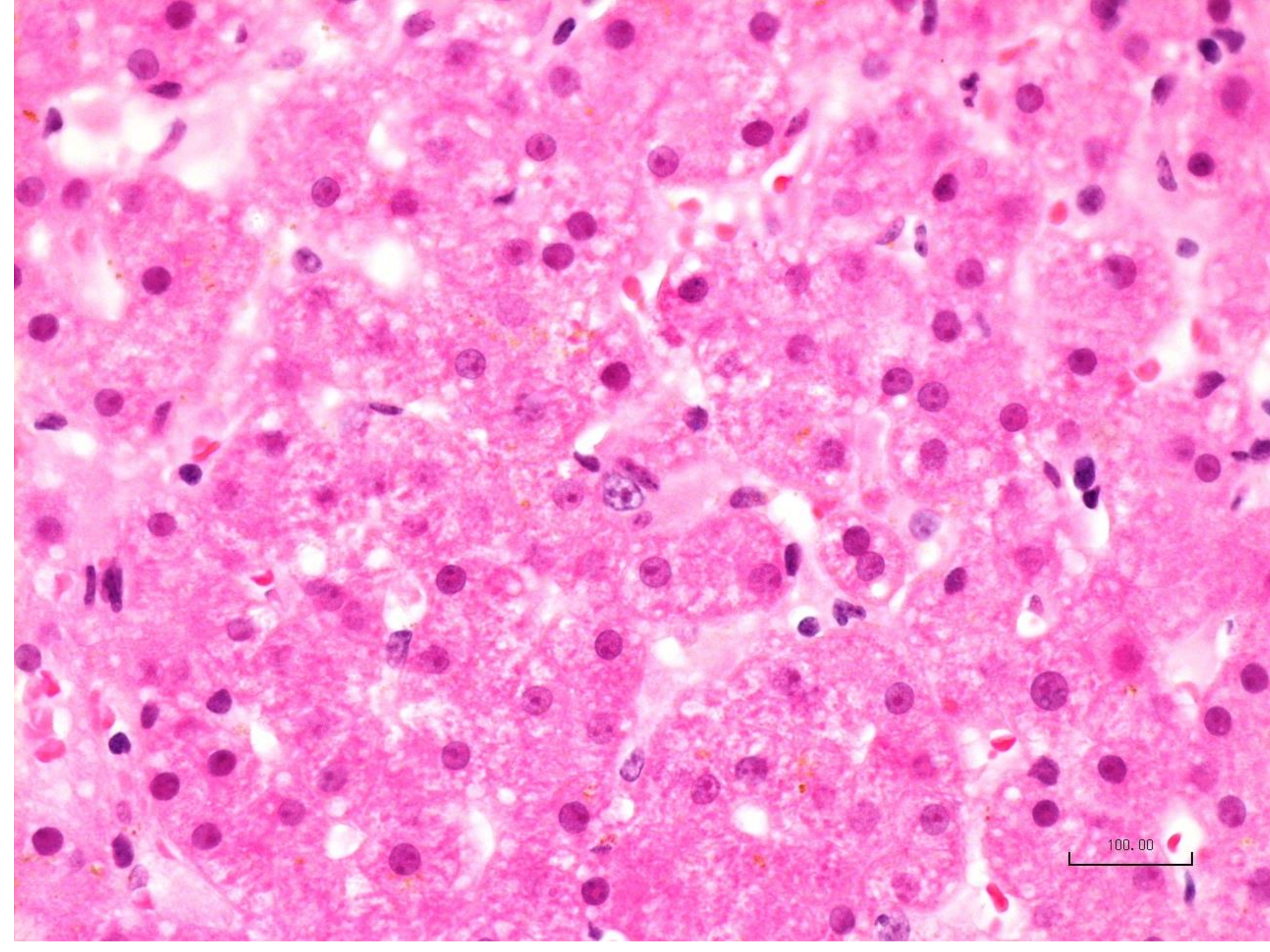
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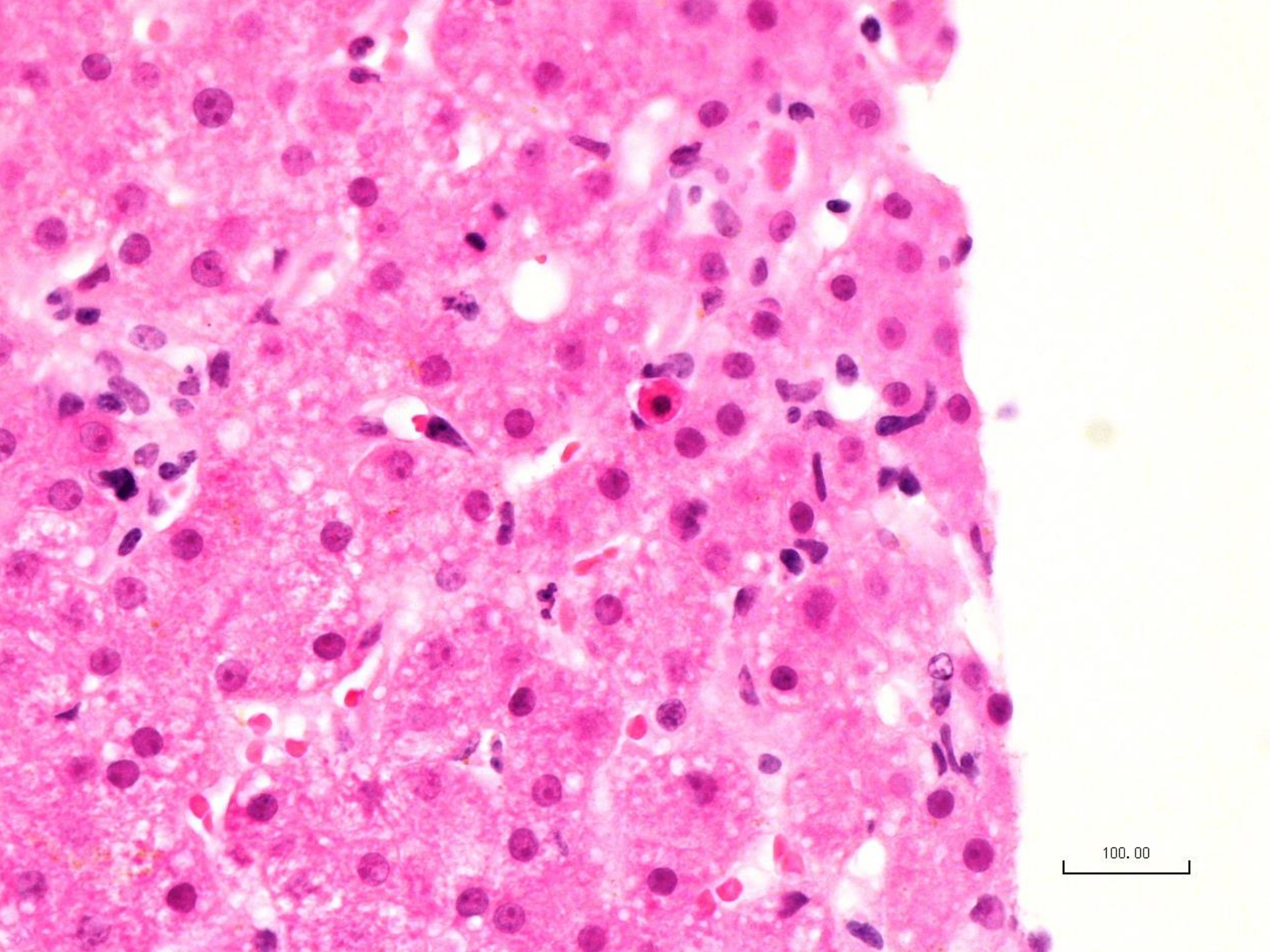


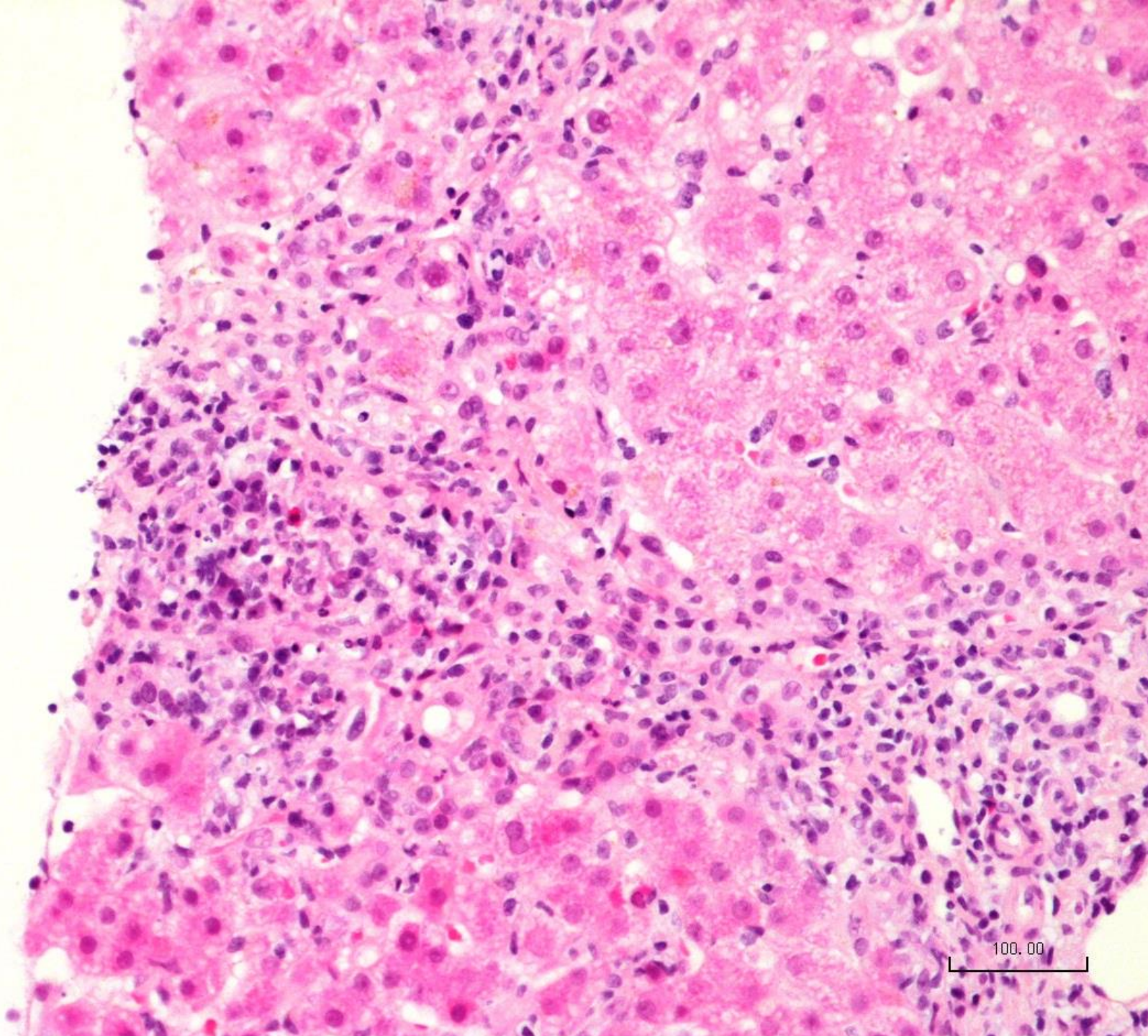
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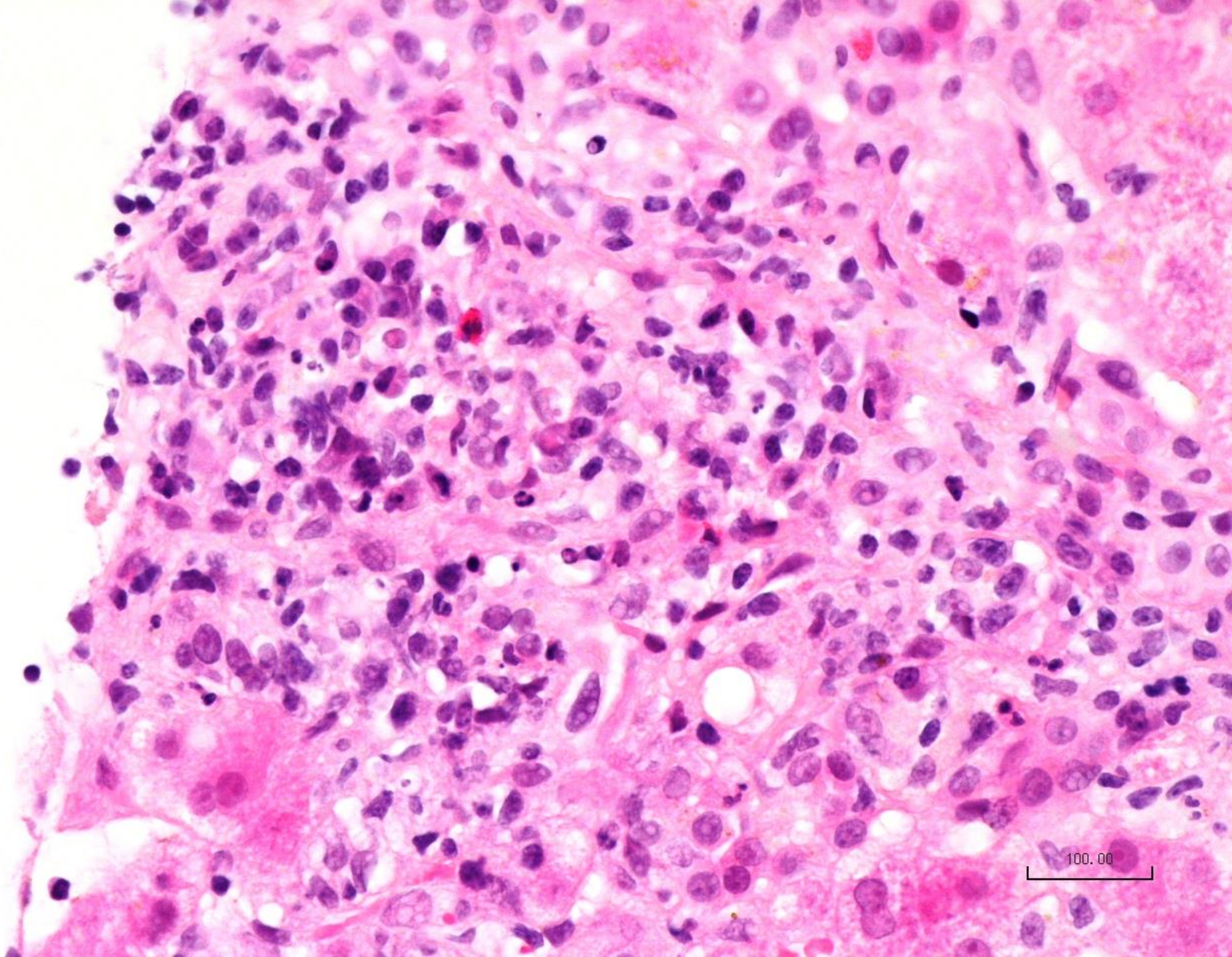
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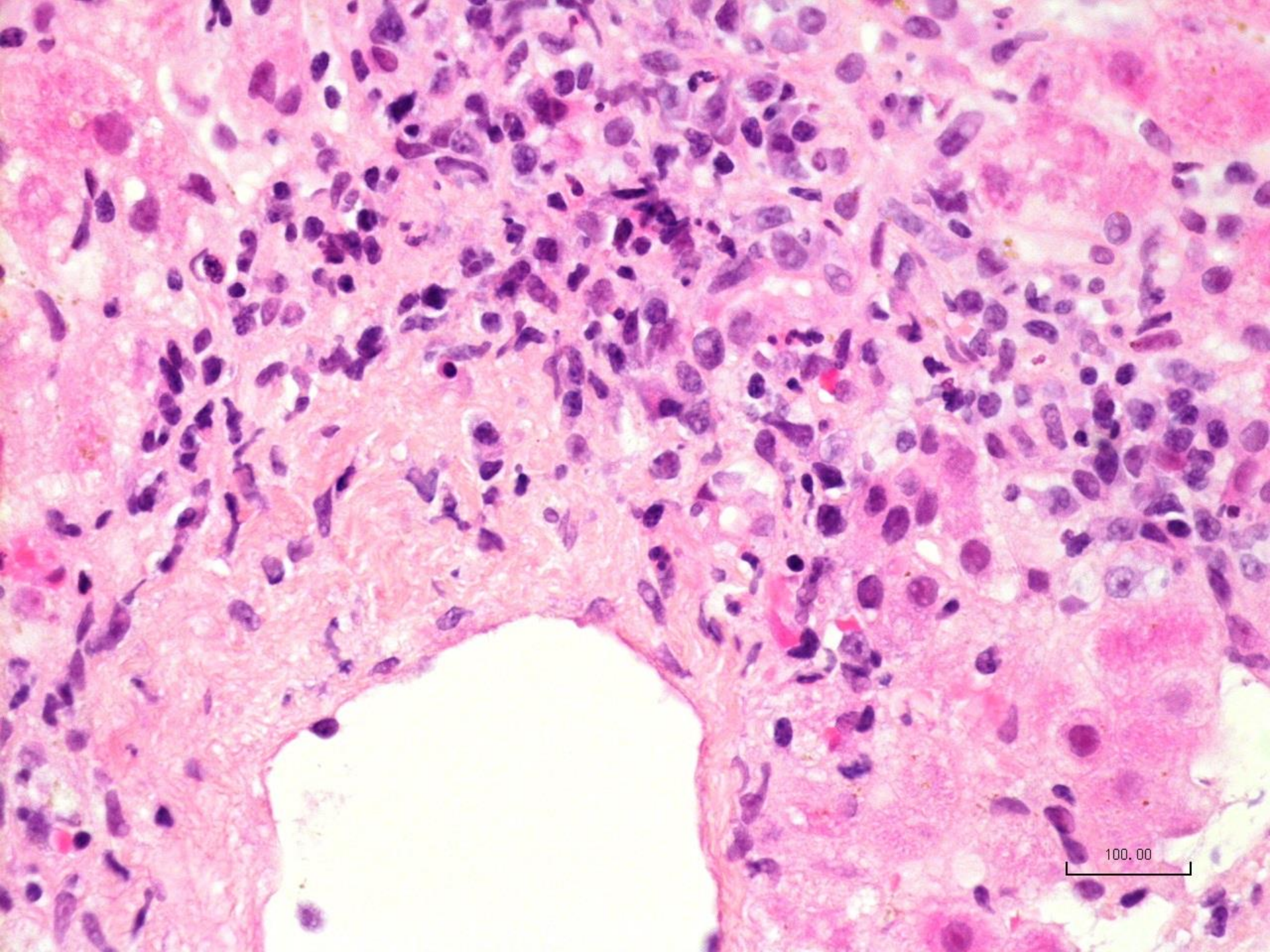




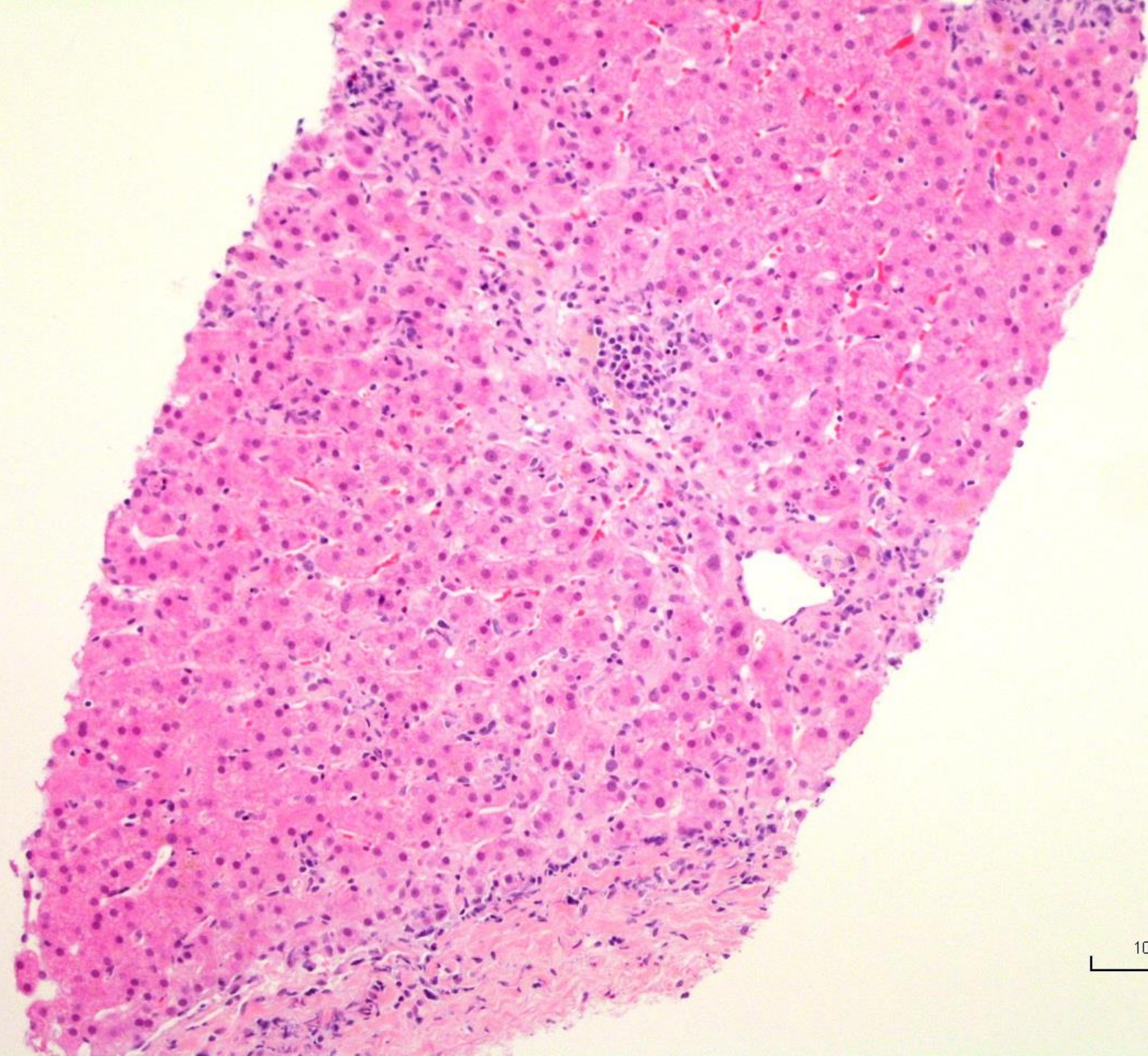


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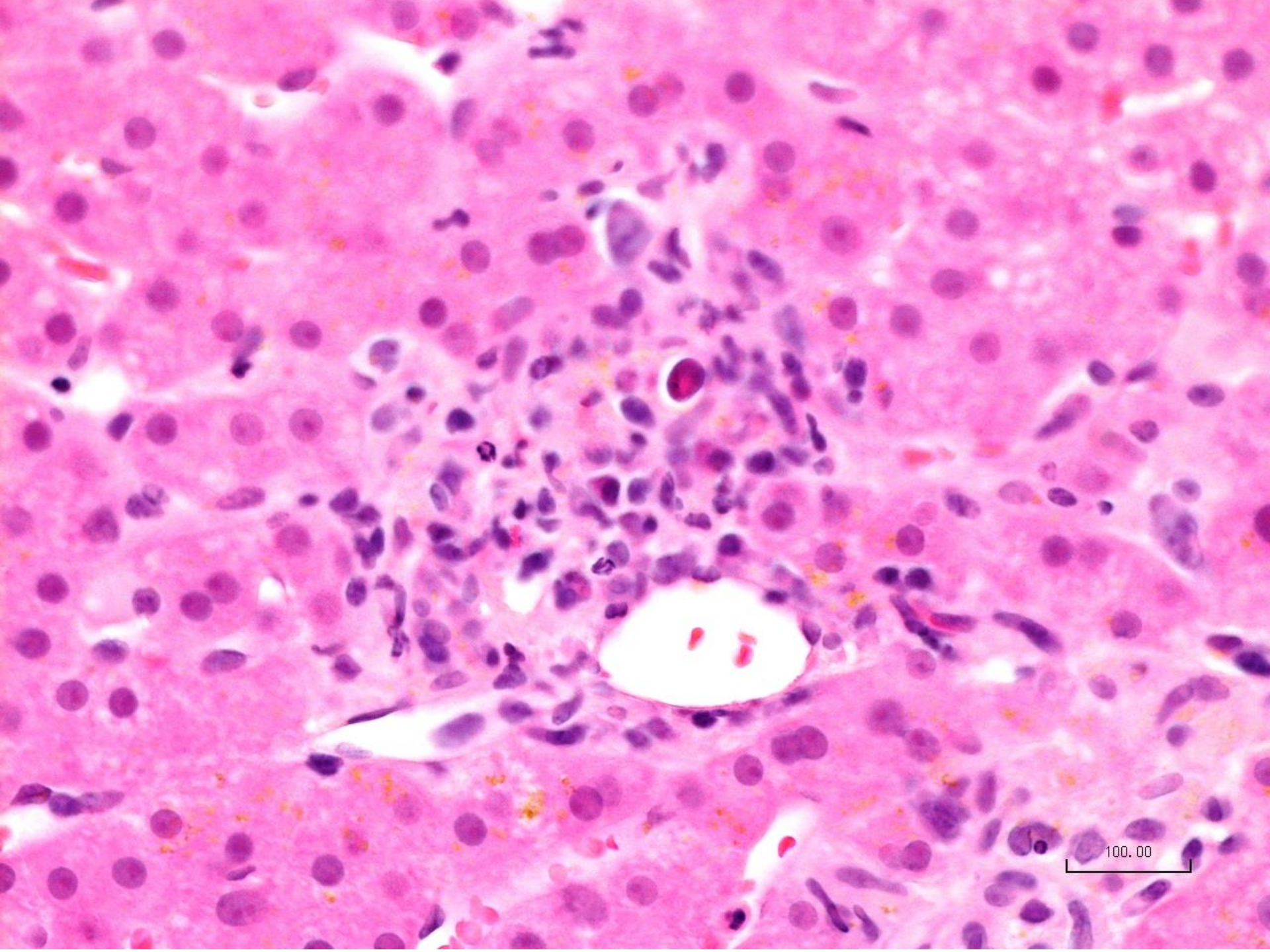


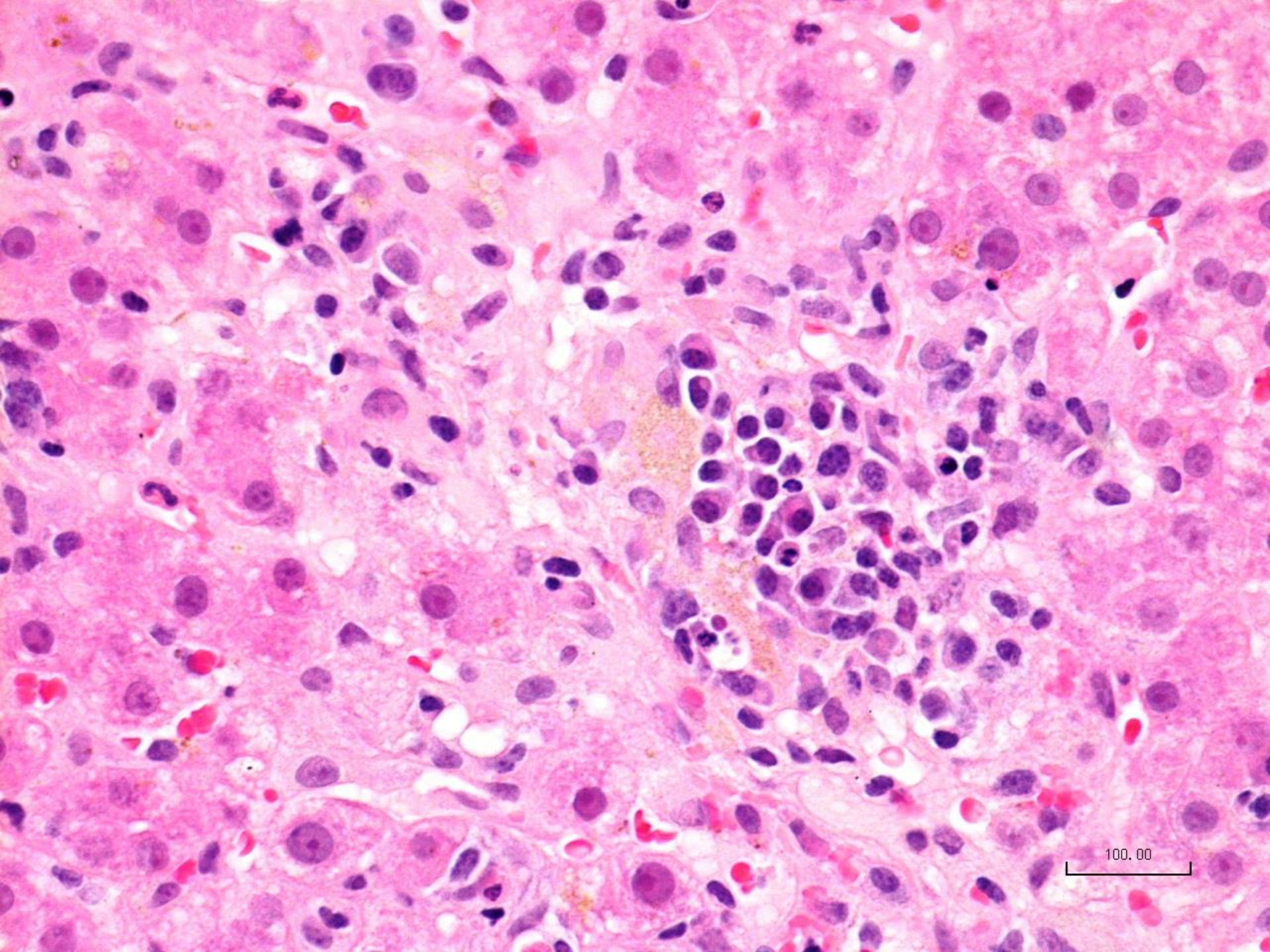


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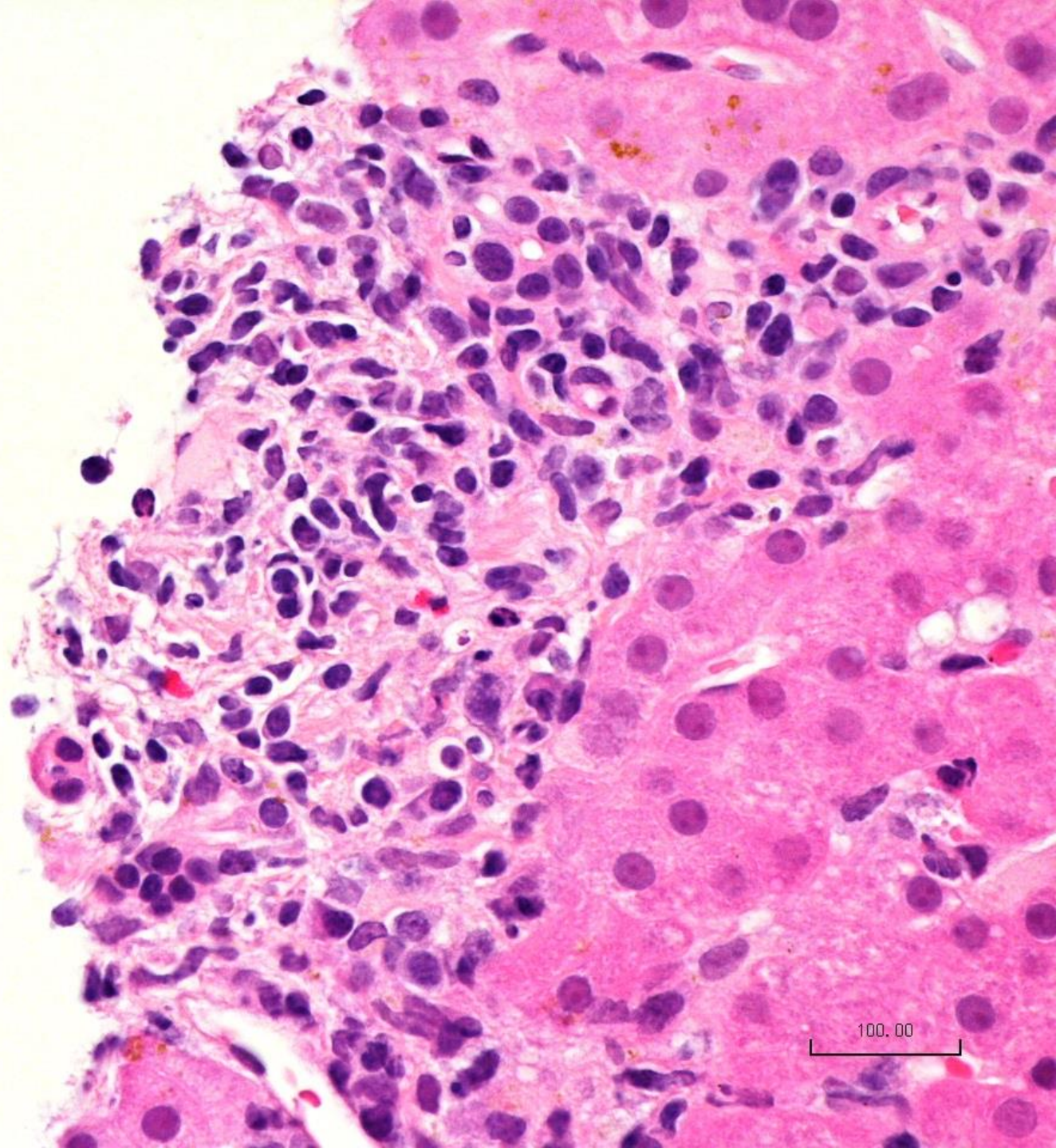


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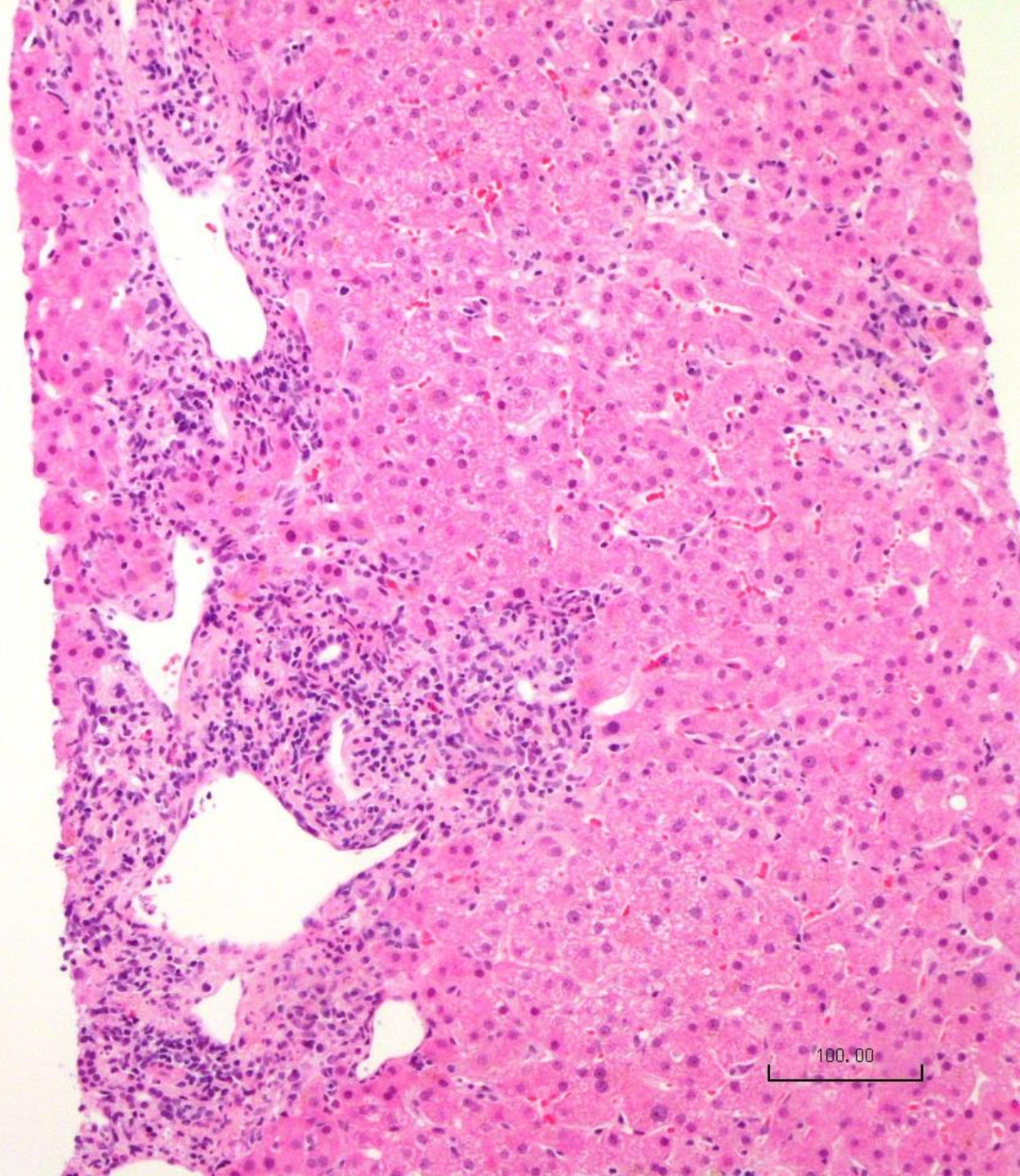




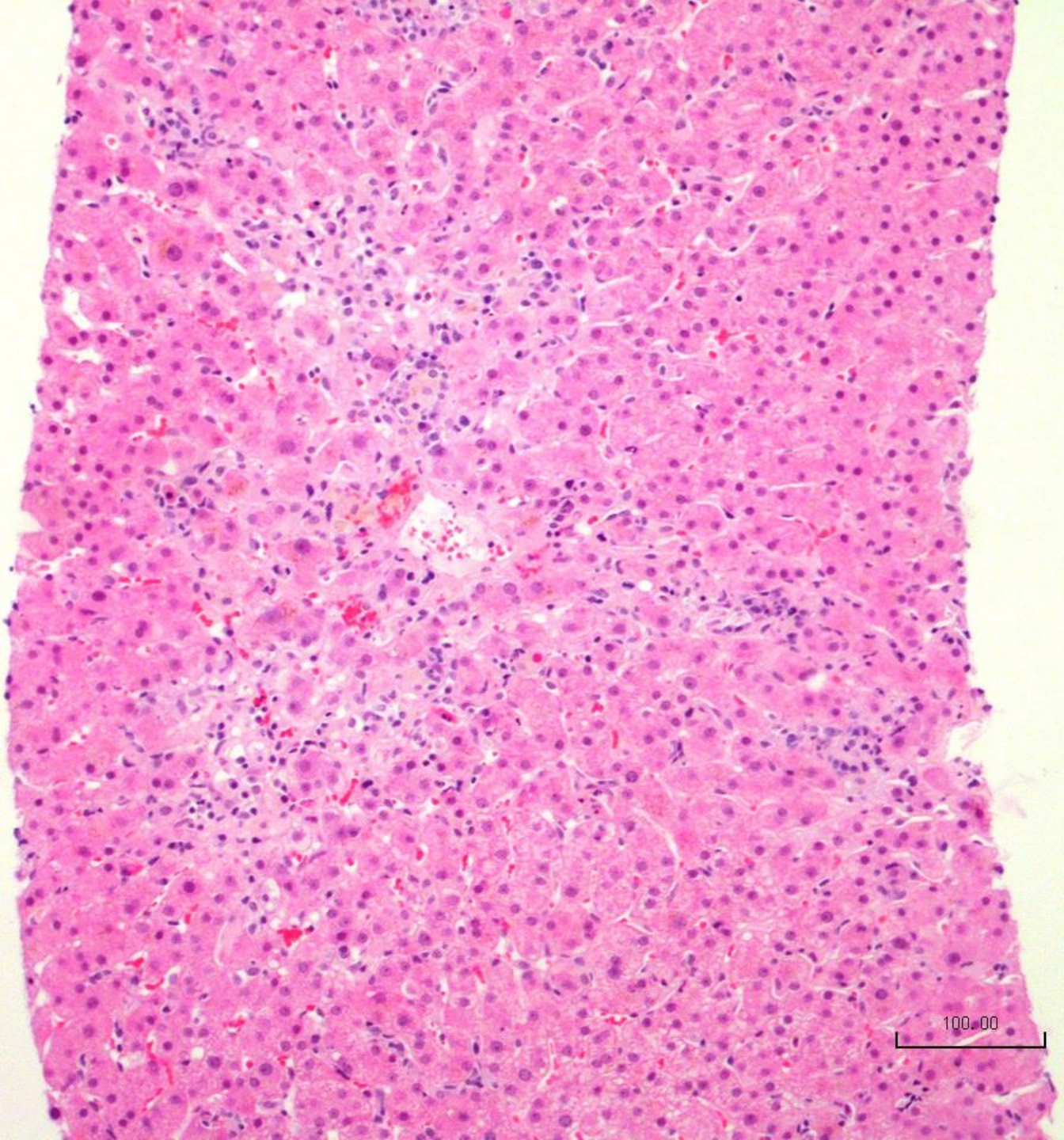
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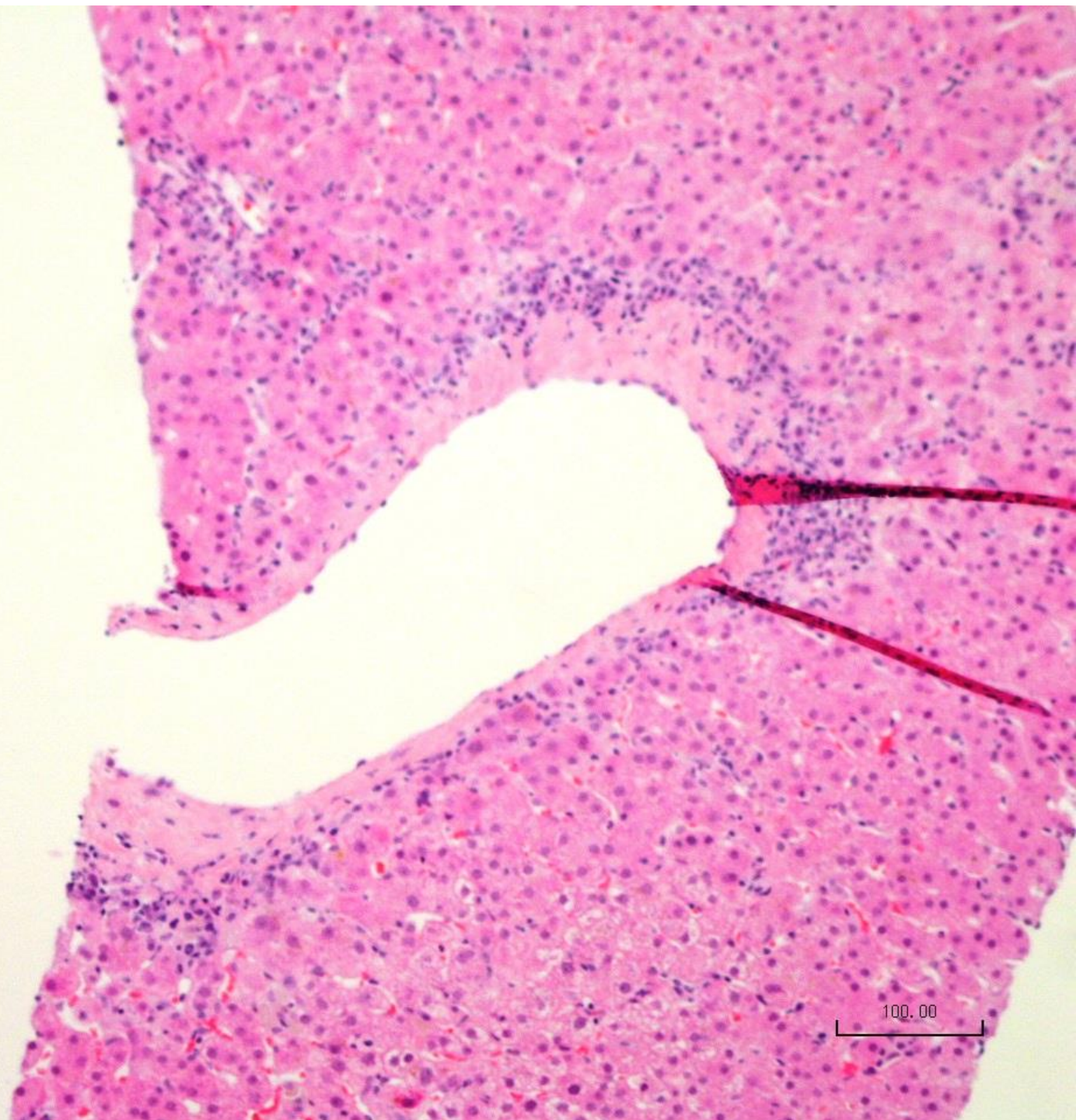
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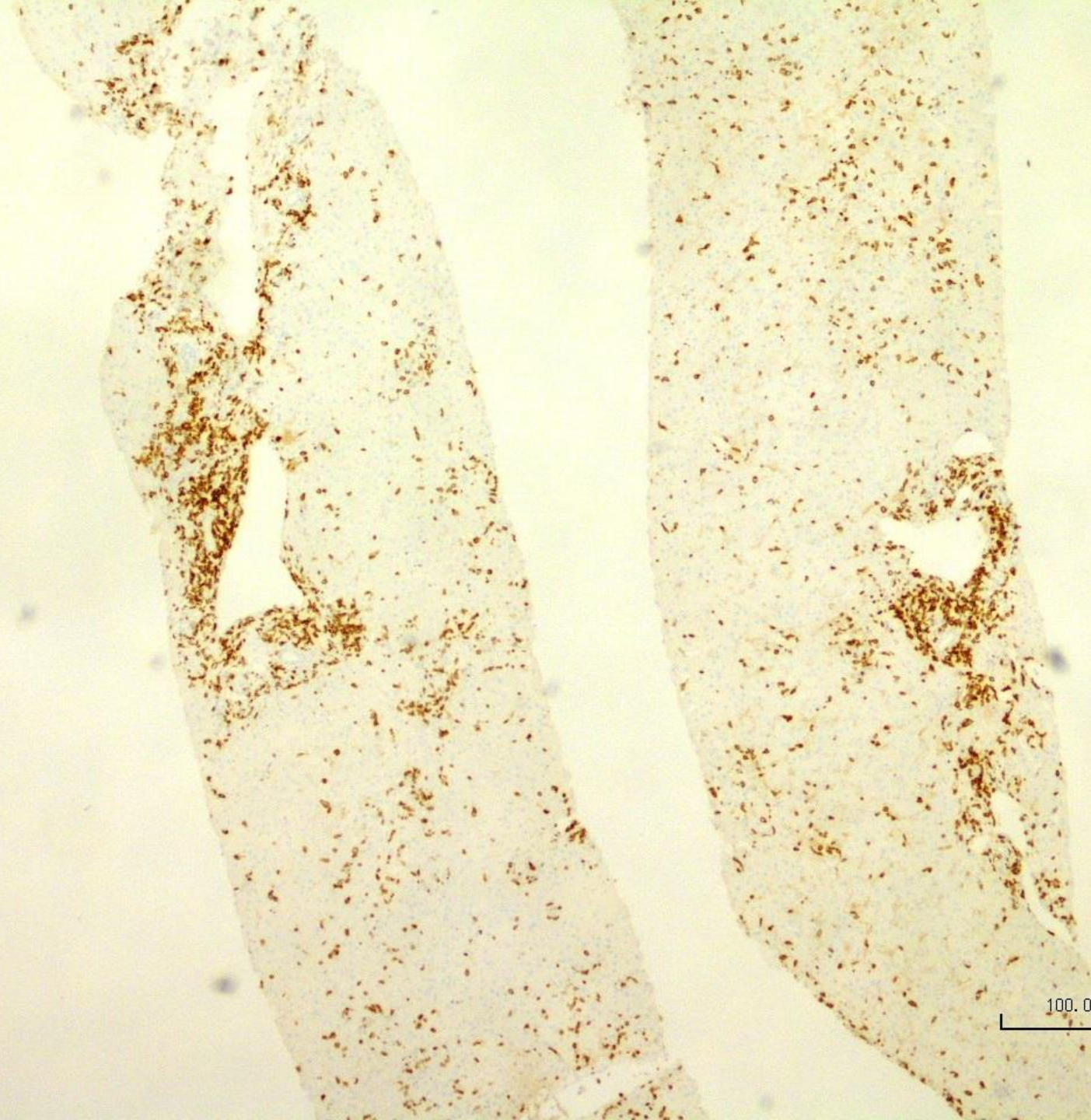


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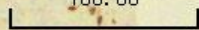


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CD3

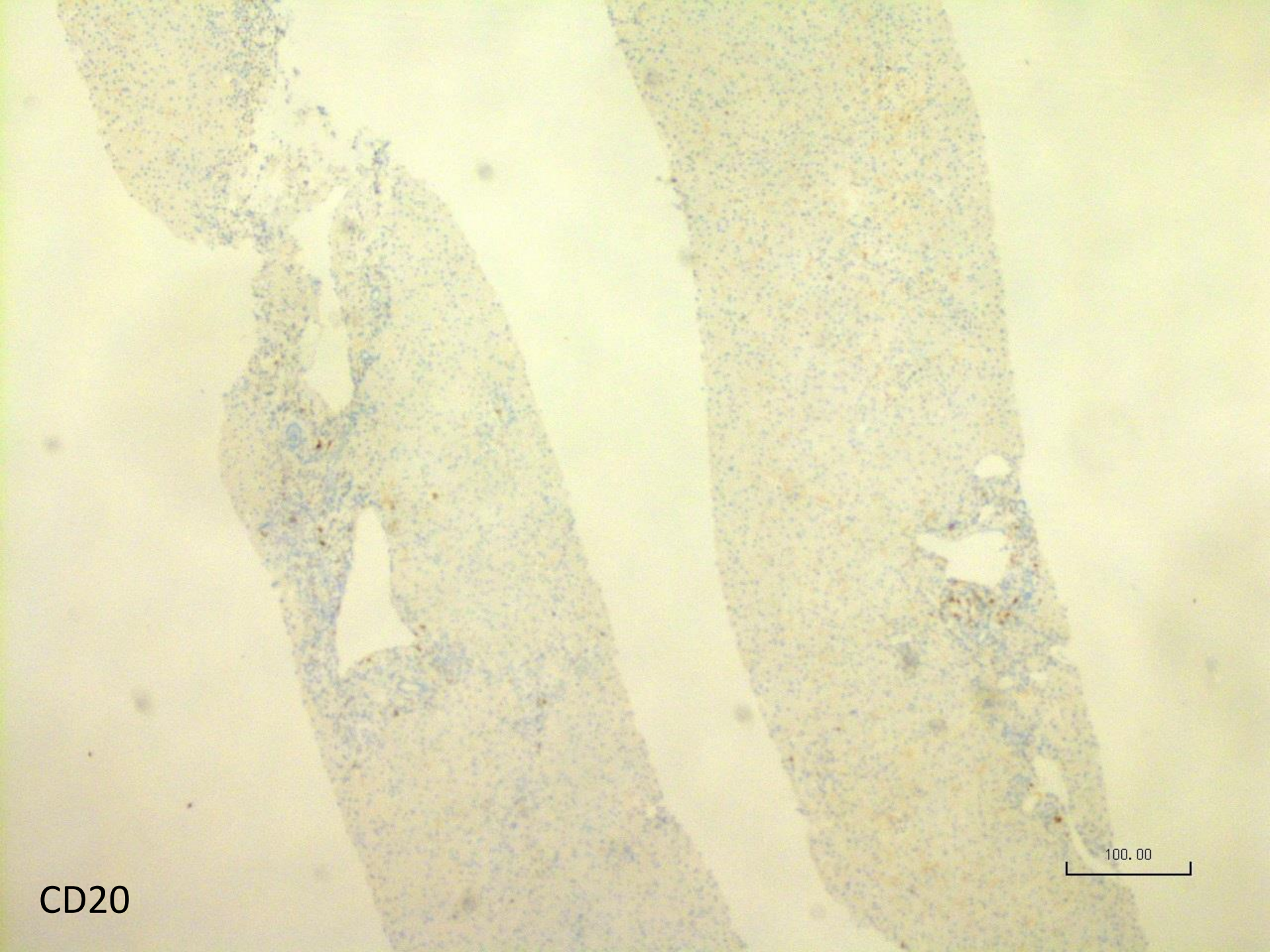
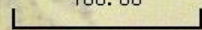


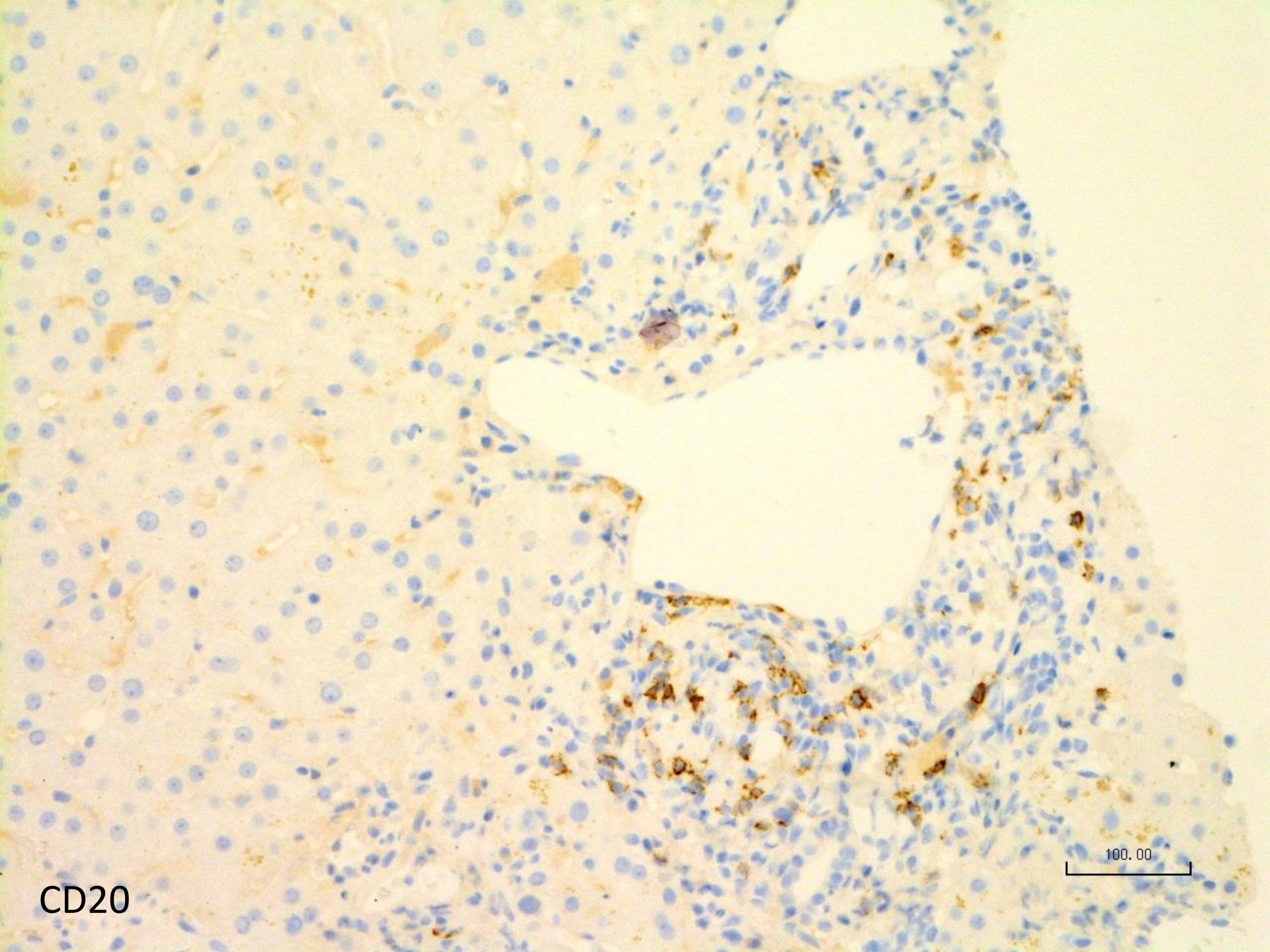
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CD20

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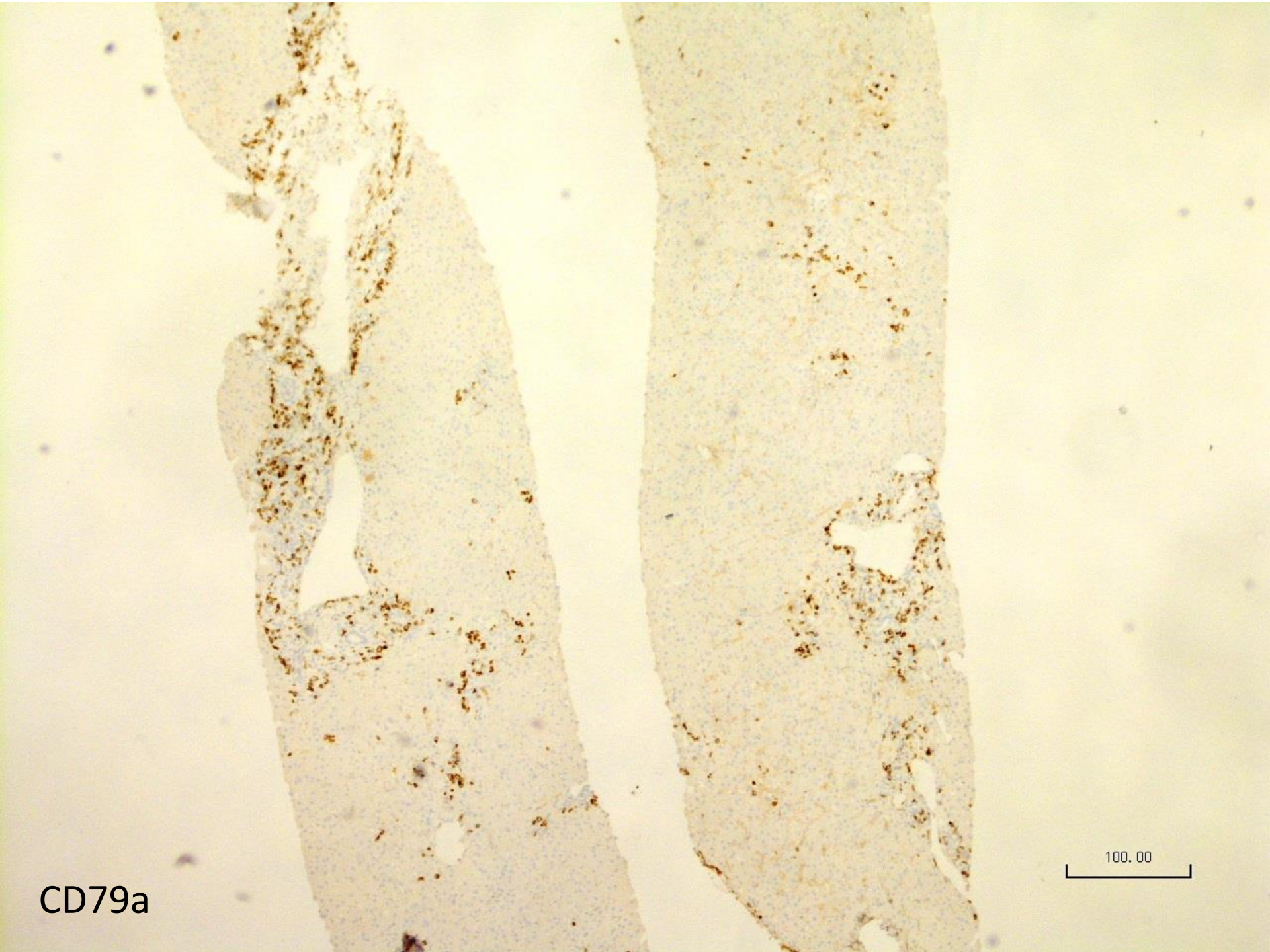
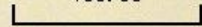


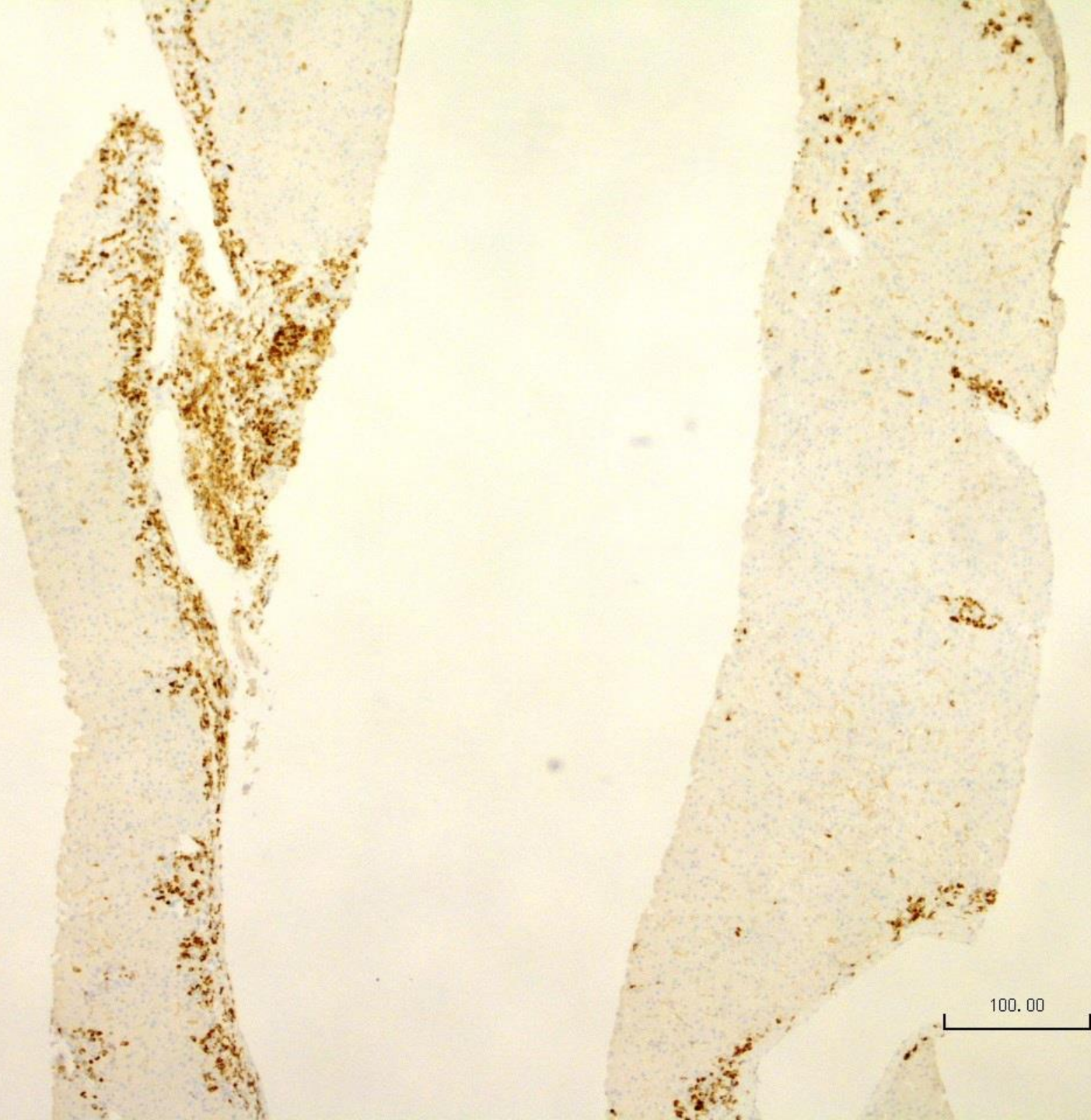
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CD79a

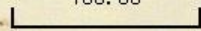
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IgG

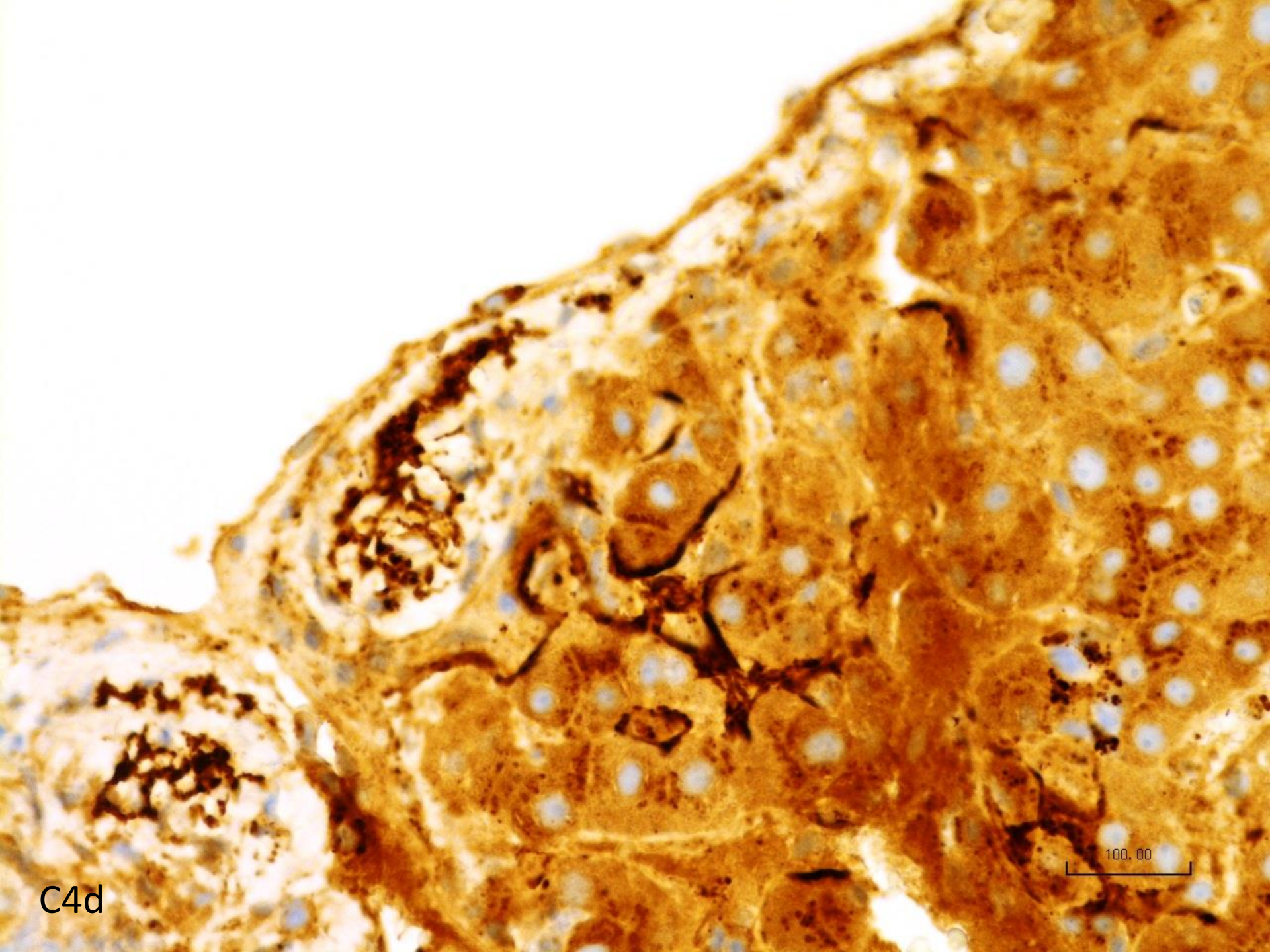
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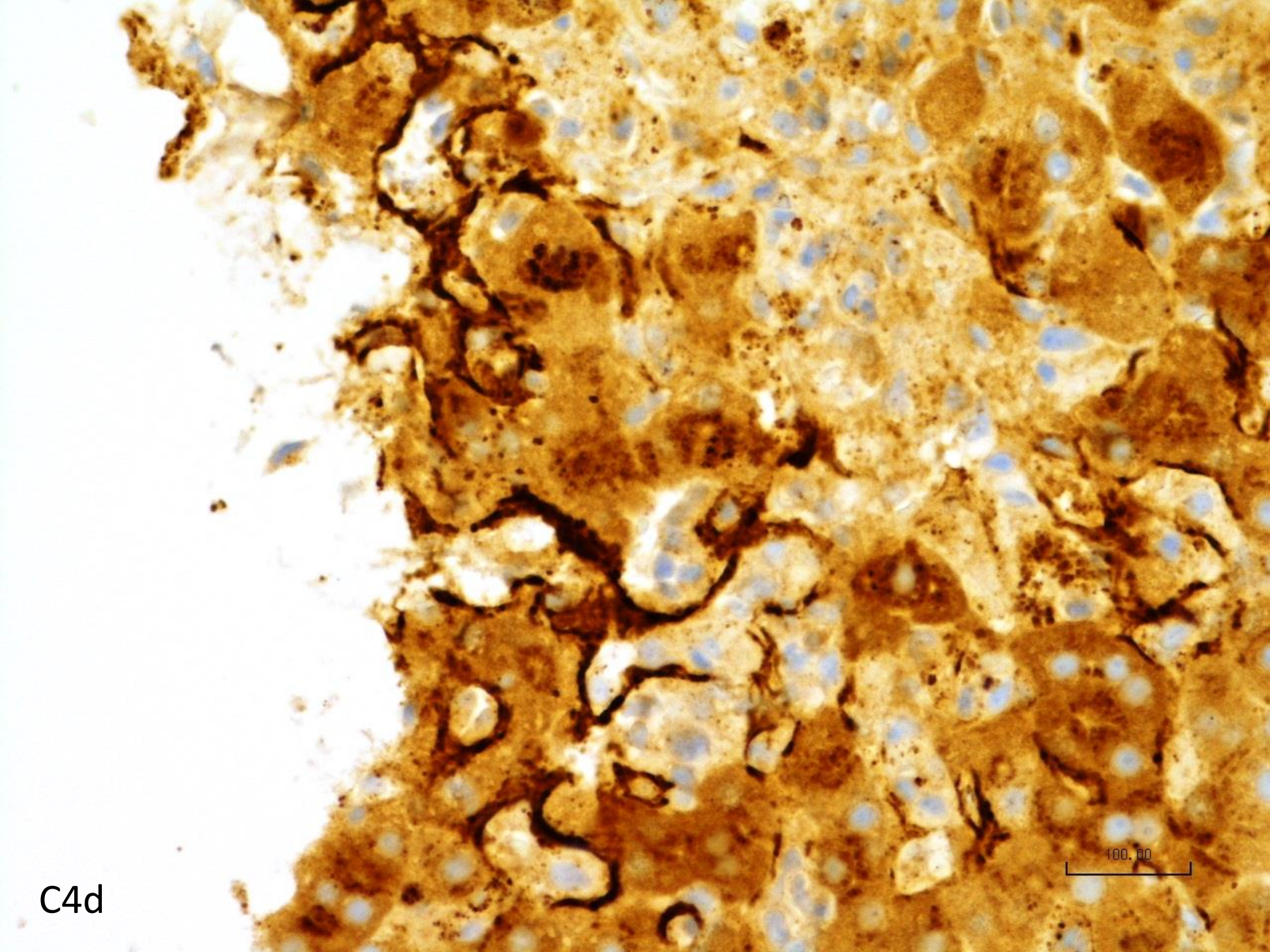
IgG4

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C4d

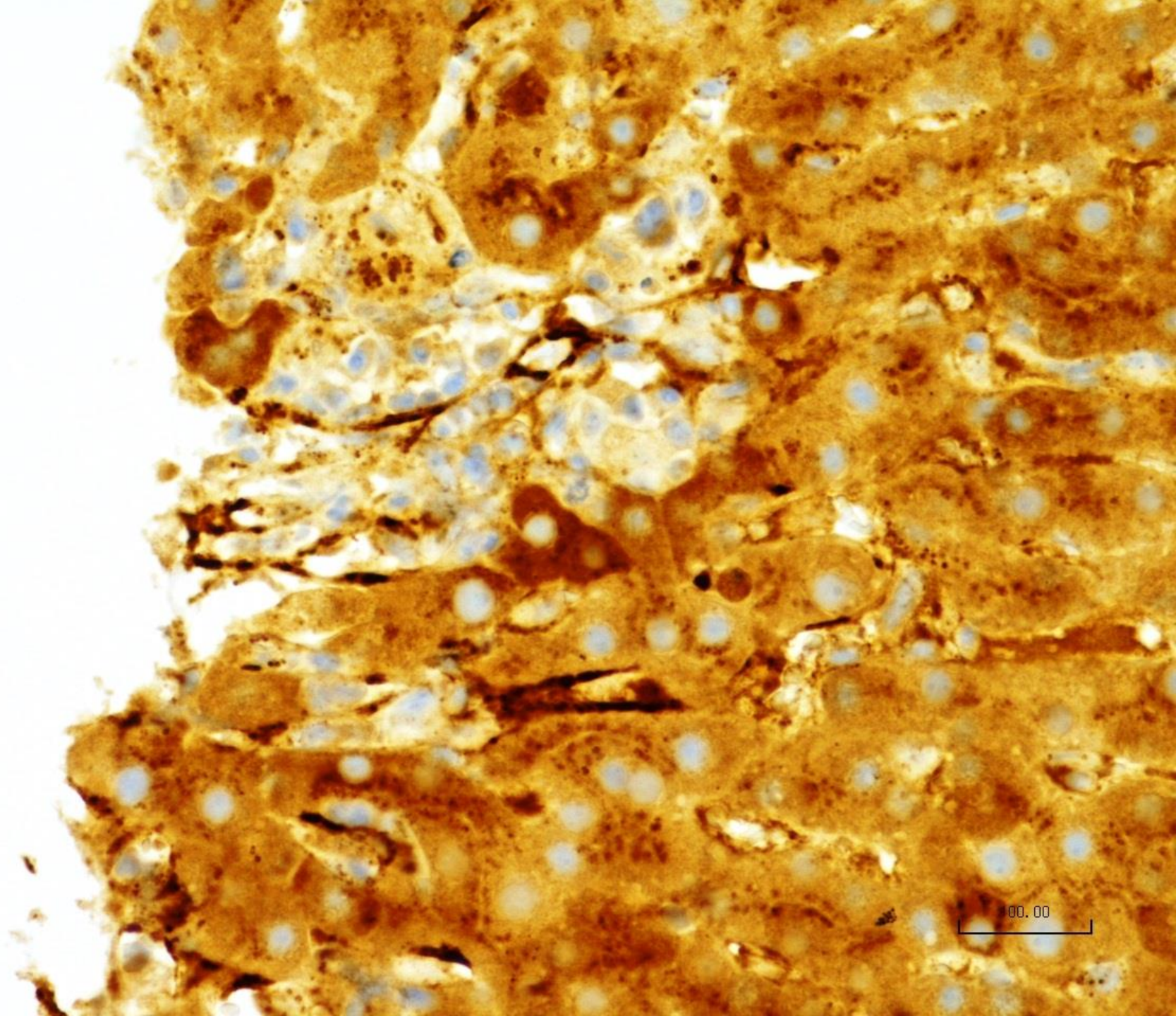
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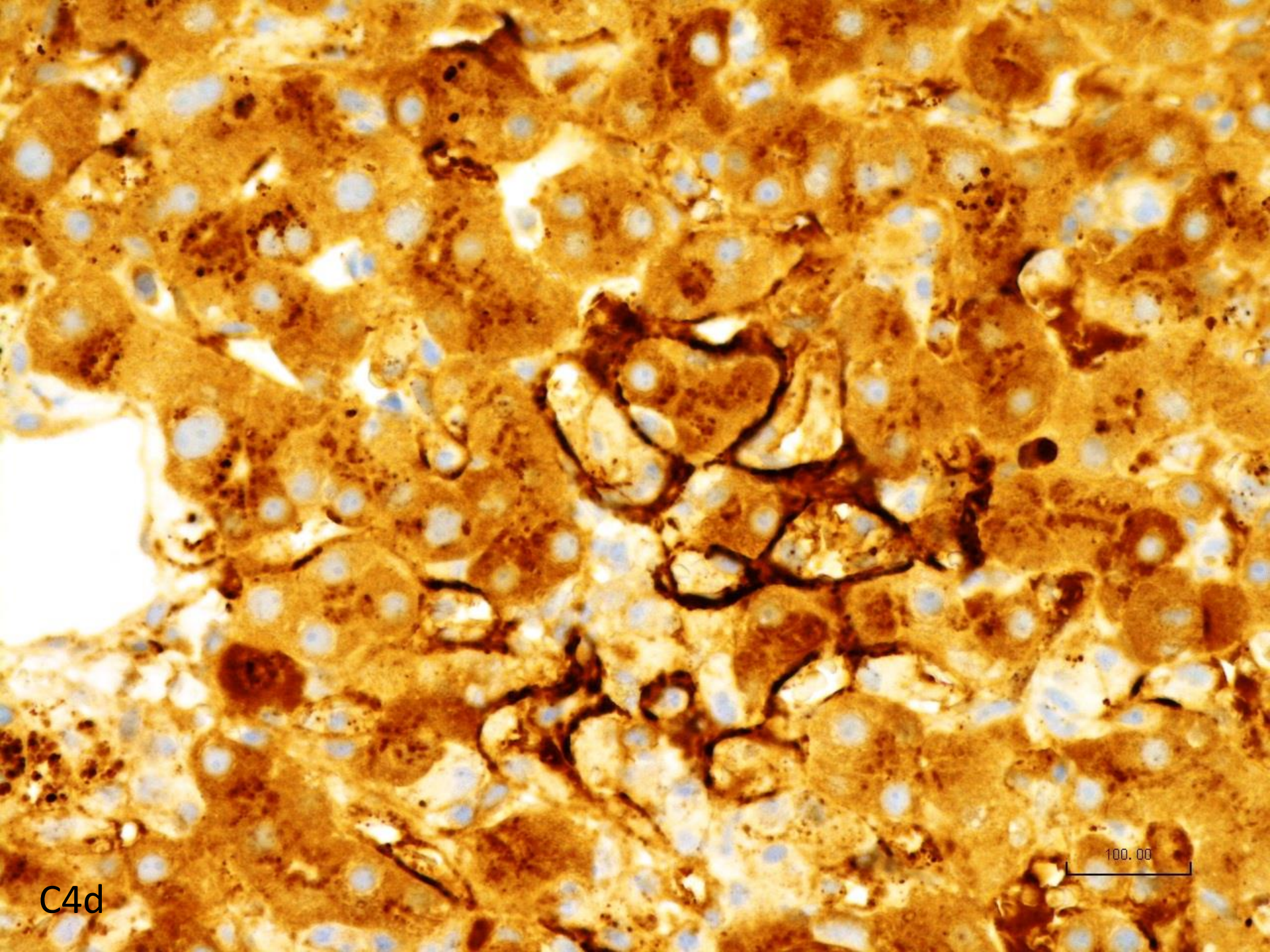
C4d

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C4d



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C4d

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- IS issues and treatment pre-biopsy
- Perivenular necrosis, central perivenulitis, endotheliitis, focal bridging necrosis, prominent plasma cells
- Moderate to severe PCR and TCMR with likely component of AMR

- Infection (HEV/CMV/EBV), de novo AIH, recurrent AILD
- ?DSA titres

- Somewhat unusual pattern of inflammation
- Favours rejection as most likely diagnosis
- Some features support TCMR, whilst others favour diagnosis of AMR
- Grading difficult using conventional Banff criteria best regarded as moderate in severity

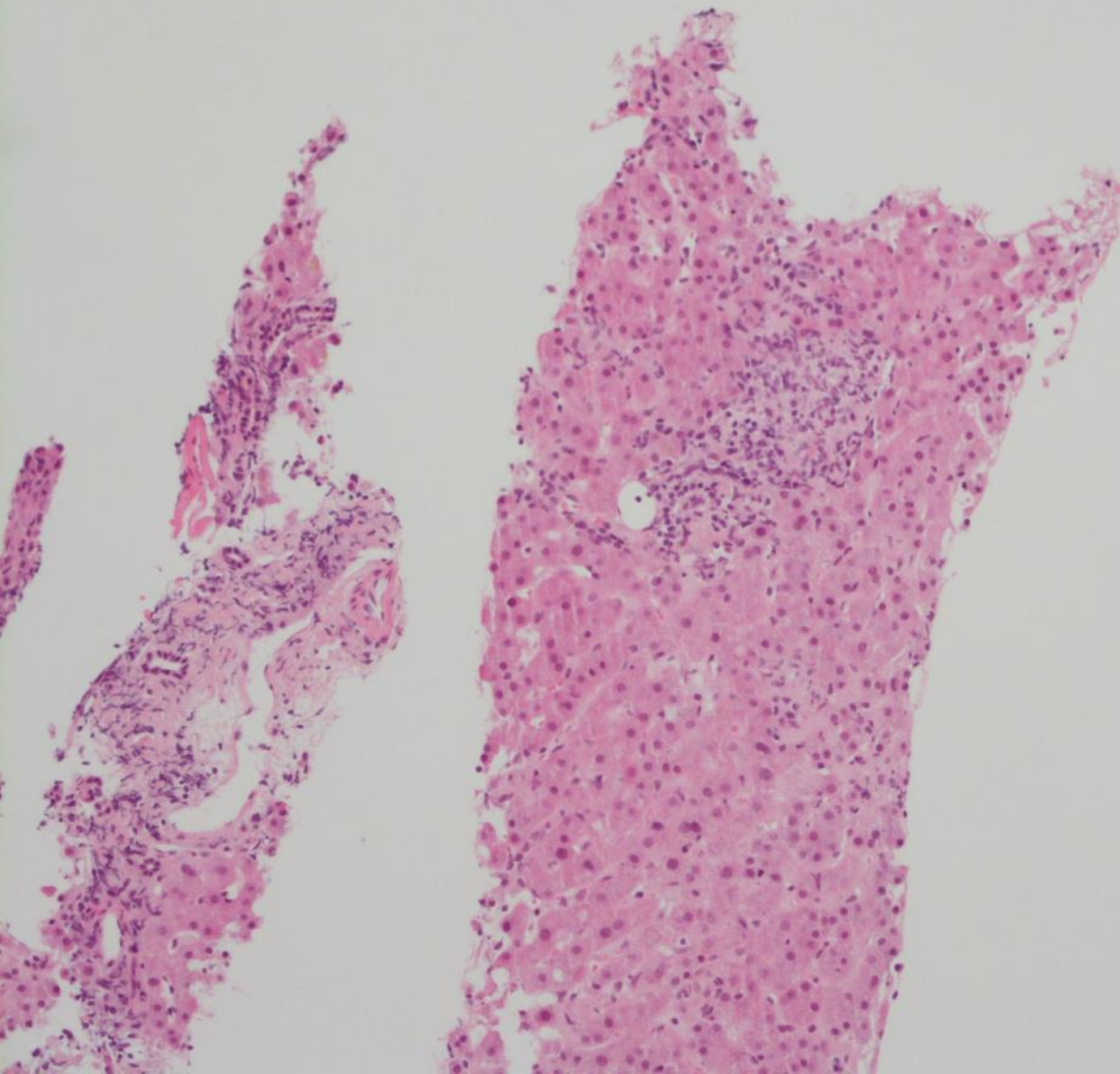
- Pulsed with Methylprednisolone after the biopsy

2nd biopsy Tues 6/04/2017 (day 80)

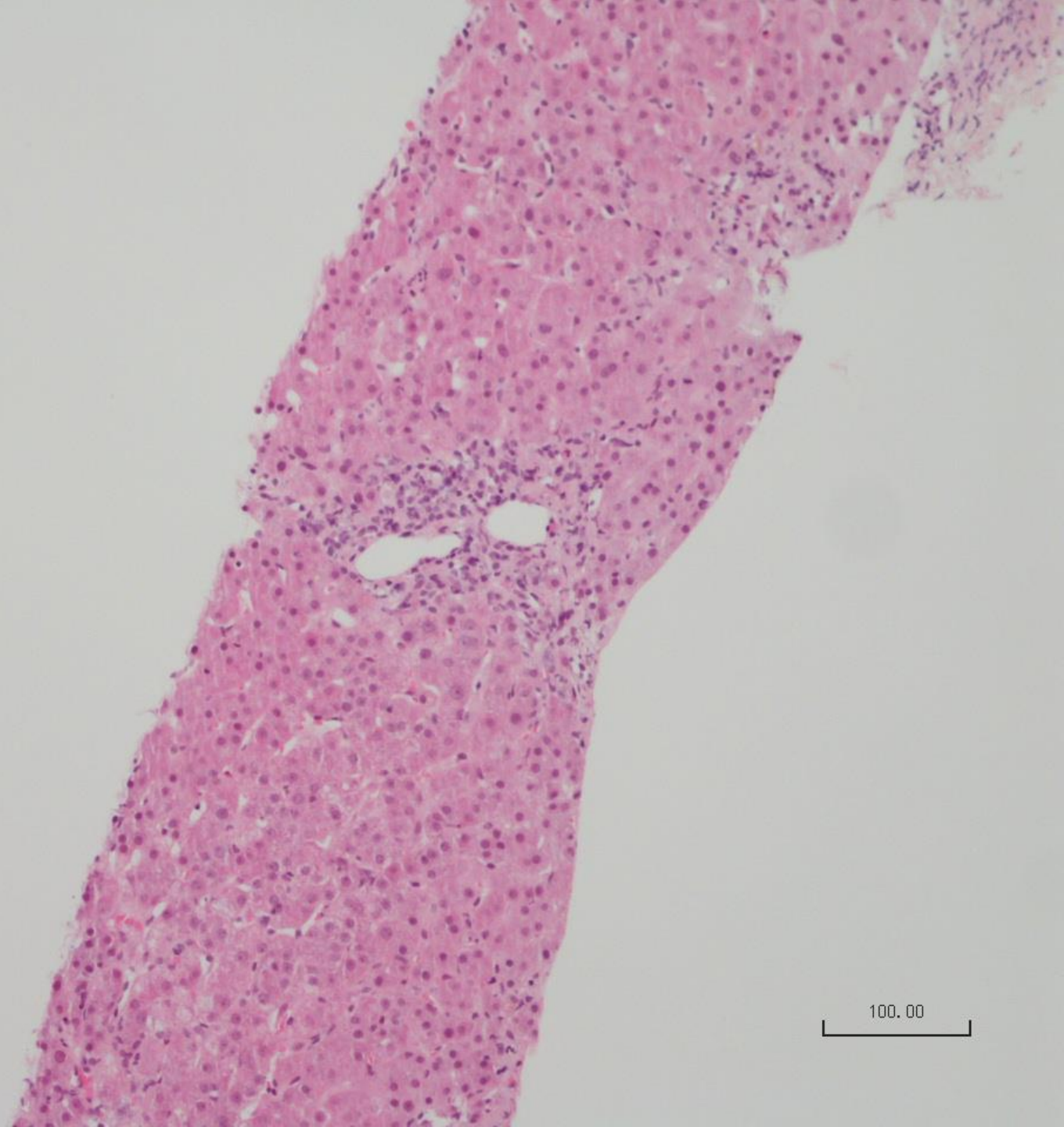
- Biopsy to rule out on-going rejection, LFTs remain increased despite pulsed methylprednisolone
- Tacrolimus levels erratic, increased to 4mg BD
- 6/04/2017:
 - Bilirubin 29
 - ALP 302
 - ALT 256
 - Tacrolimus 2.3



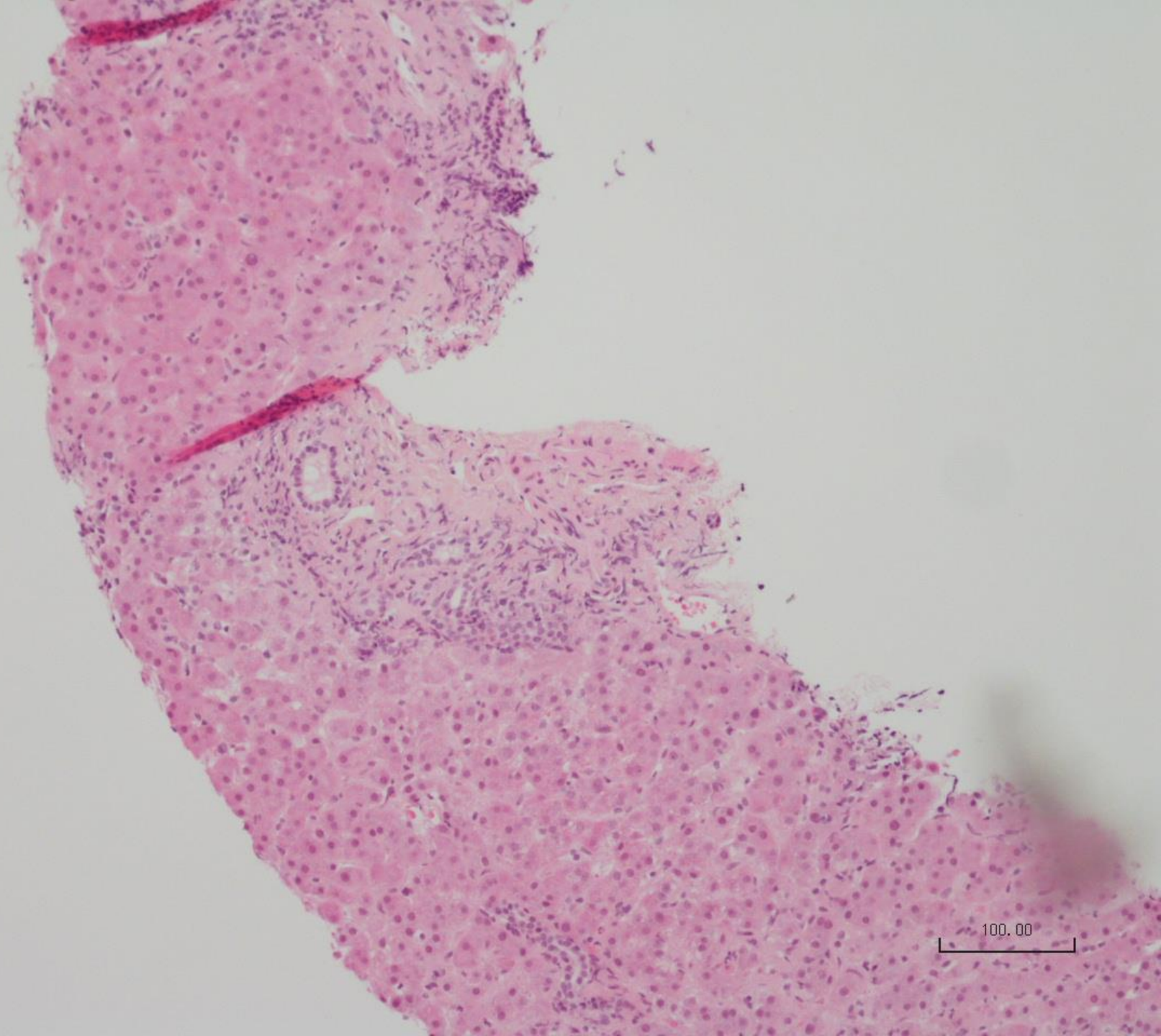
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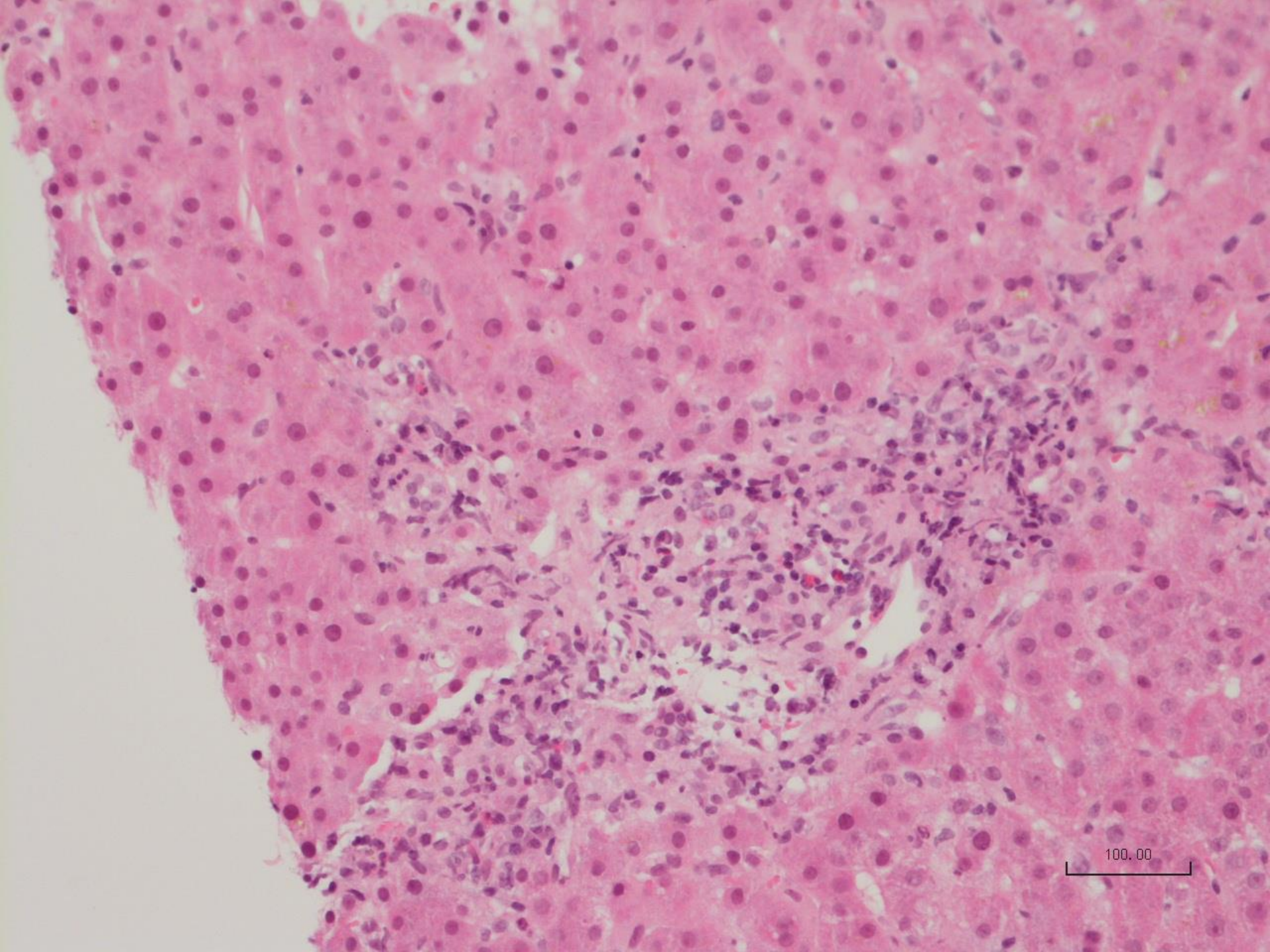
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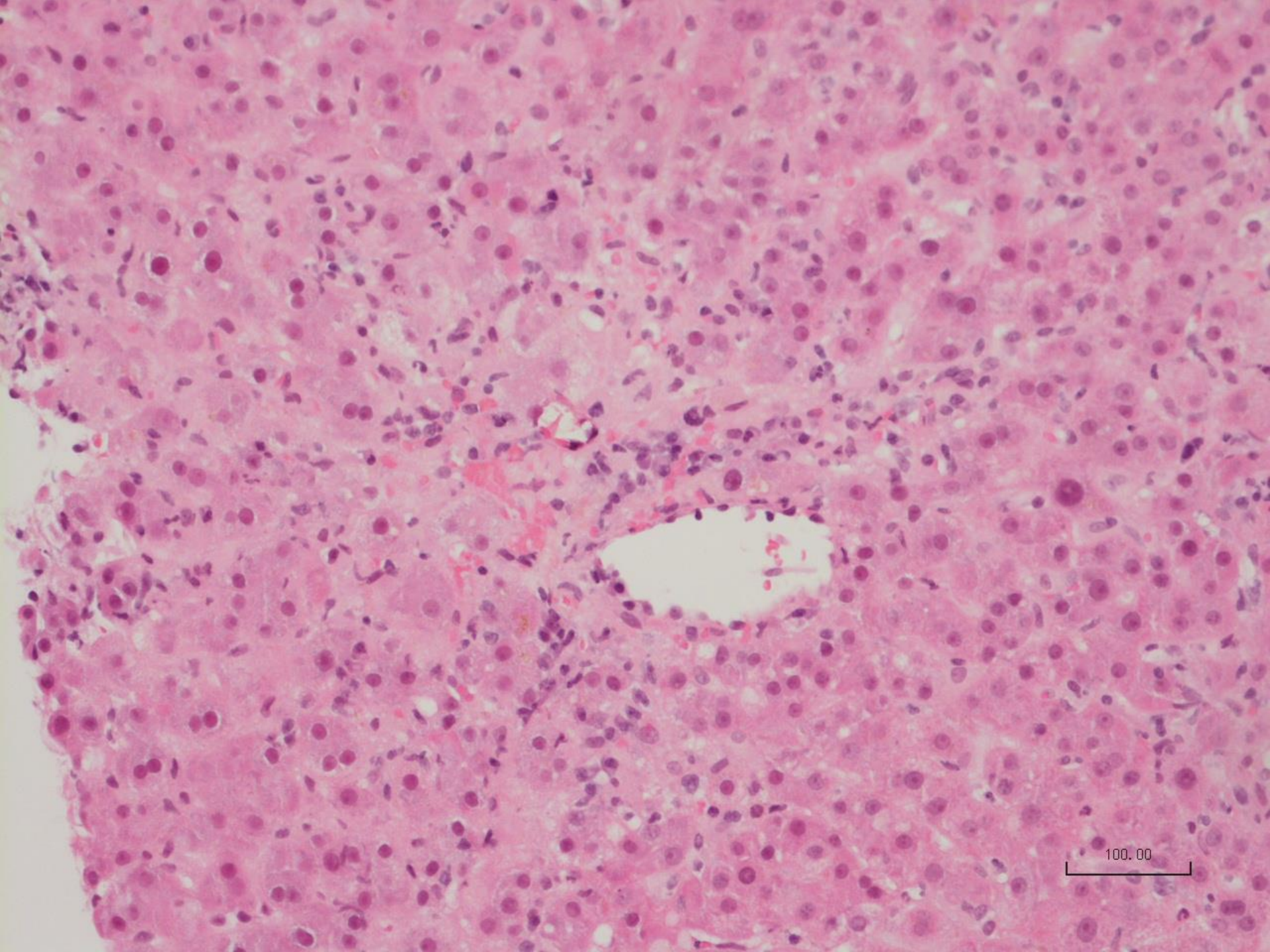


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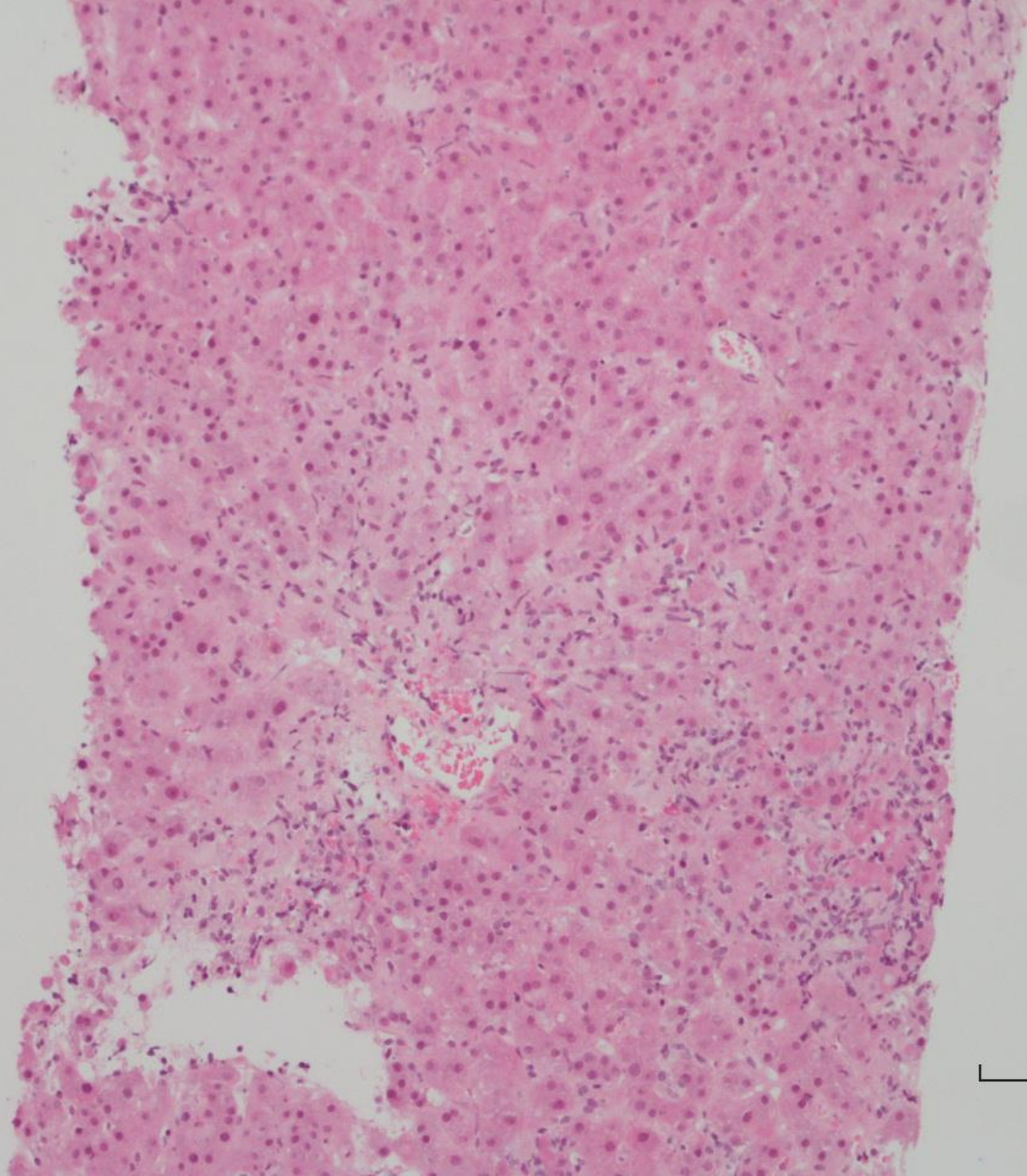


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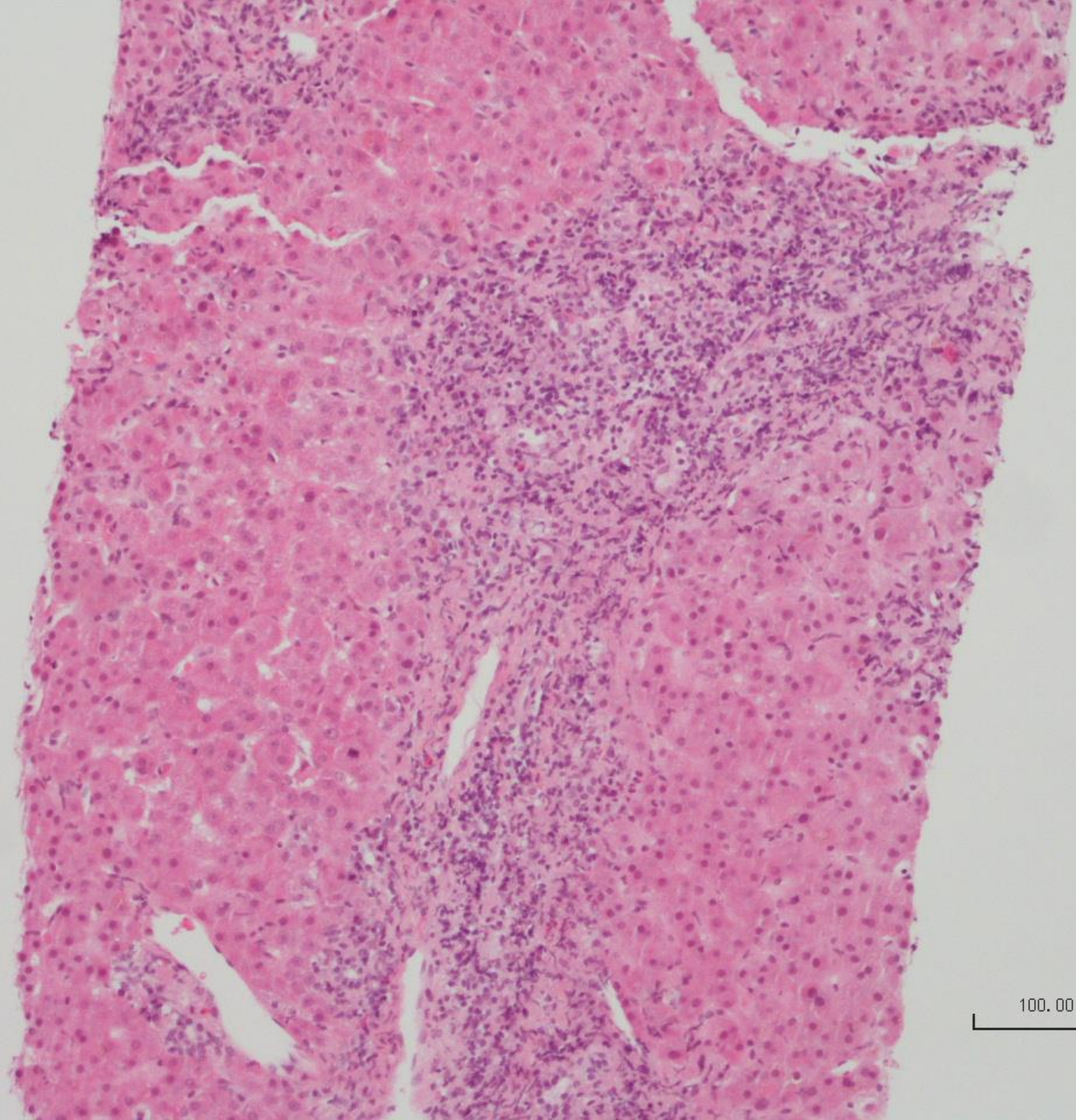




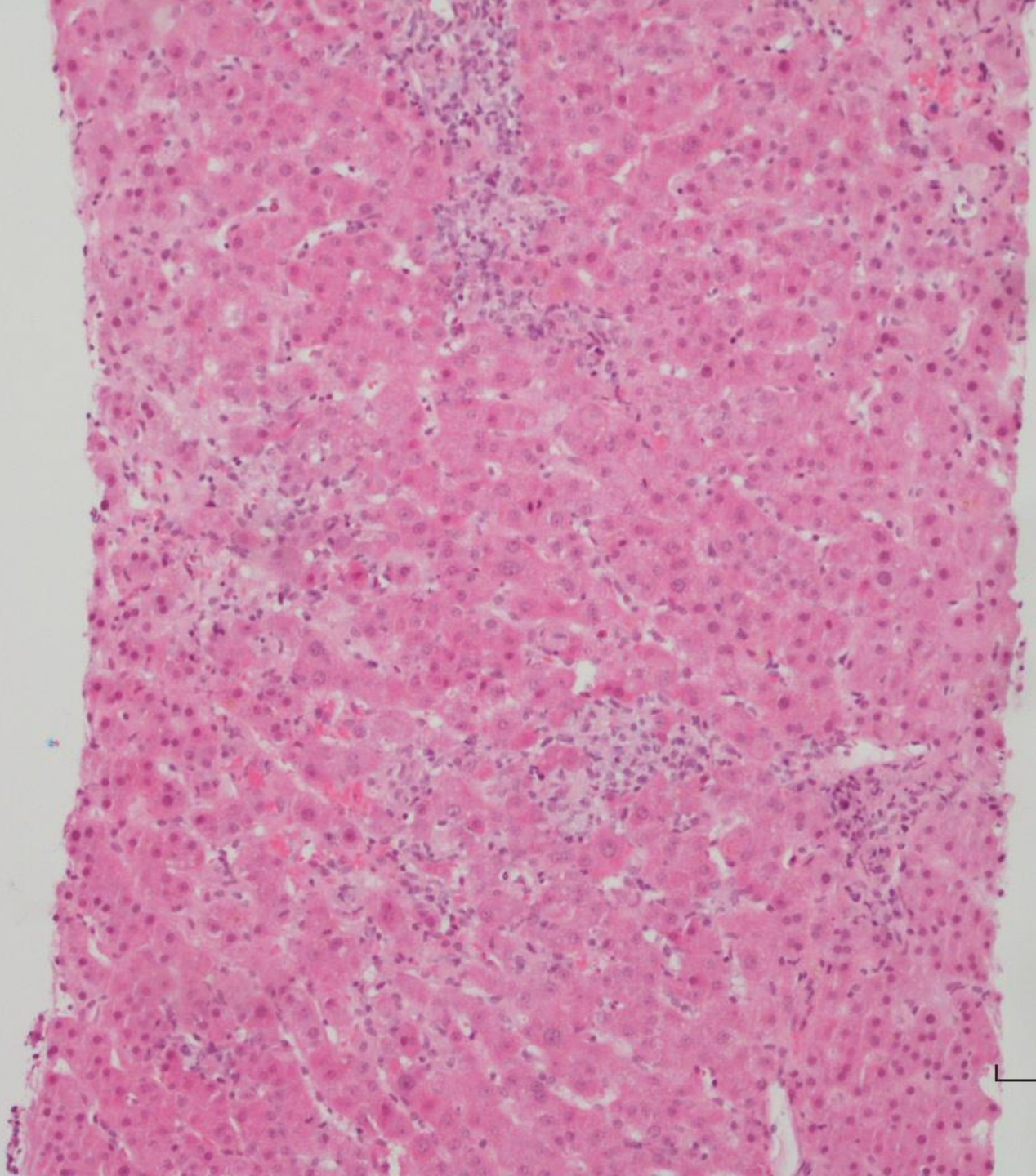
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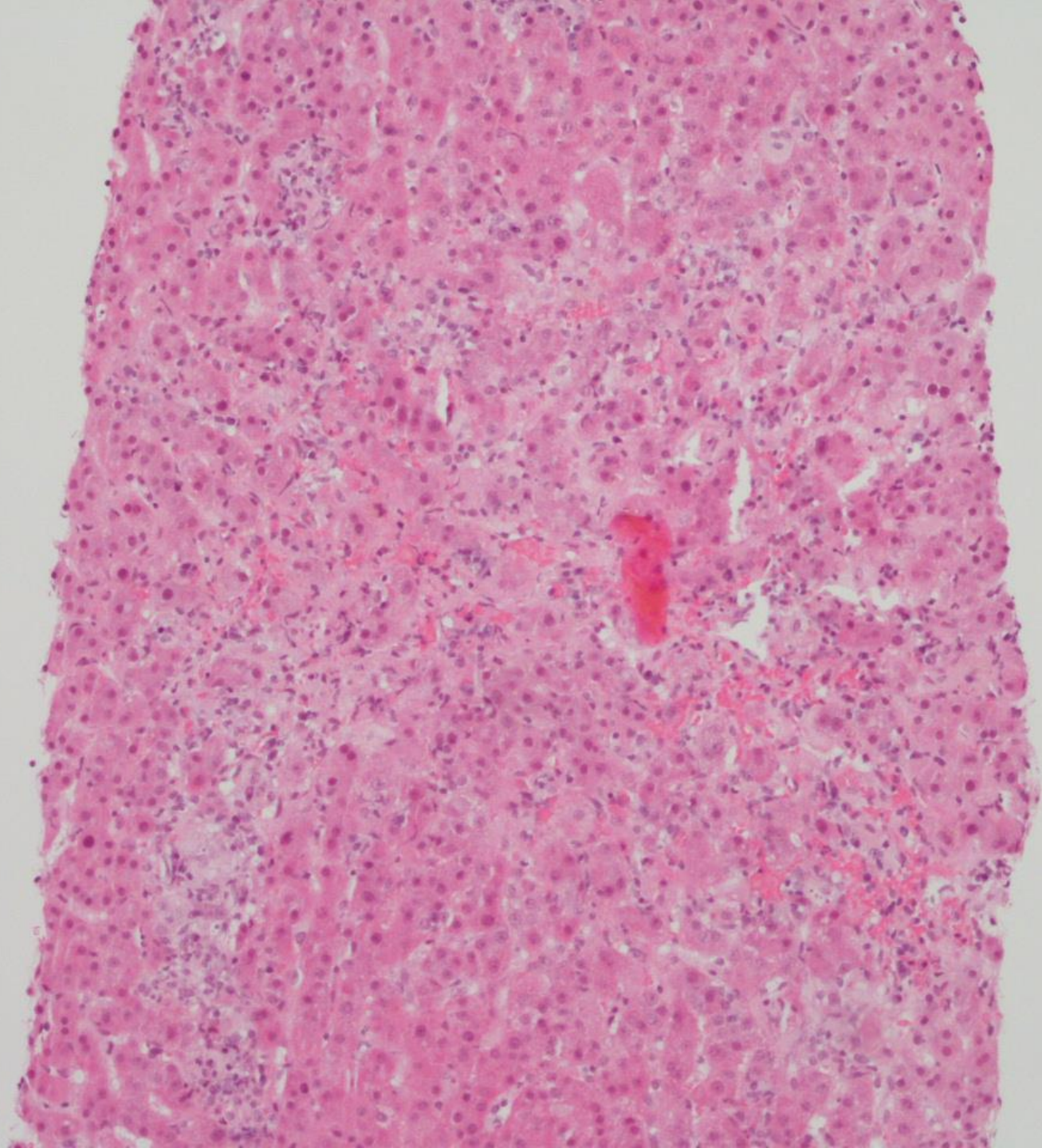
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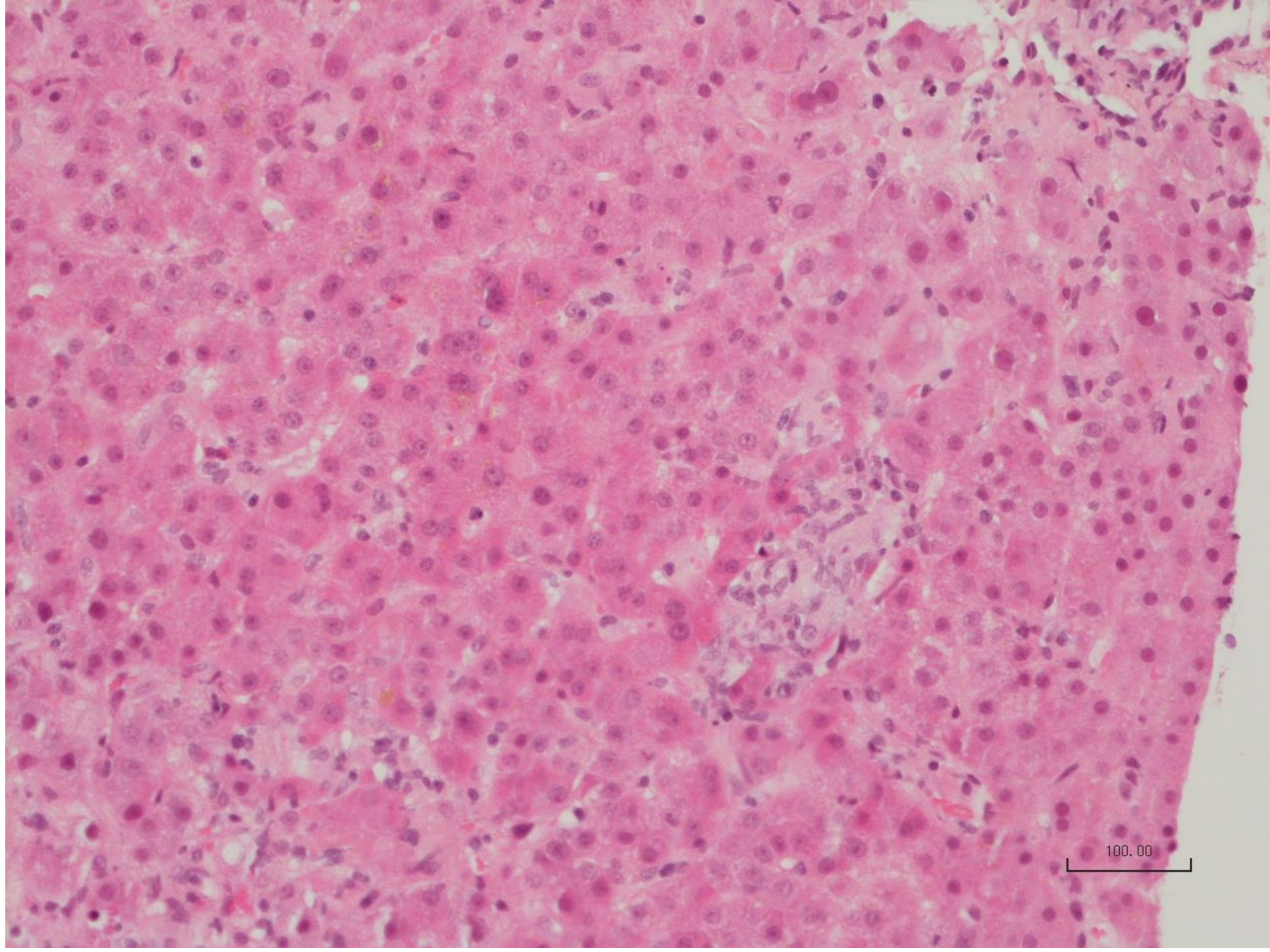


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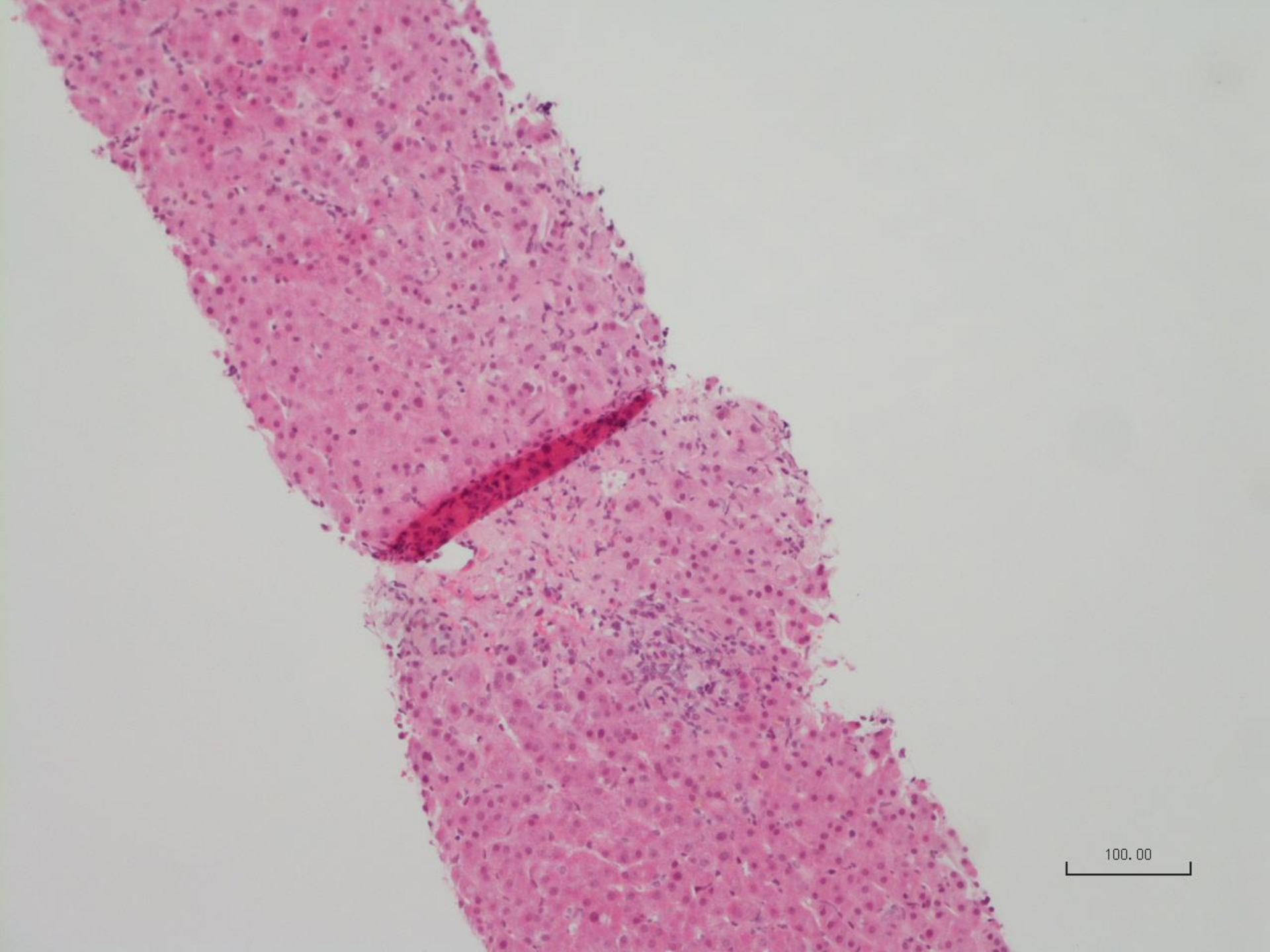


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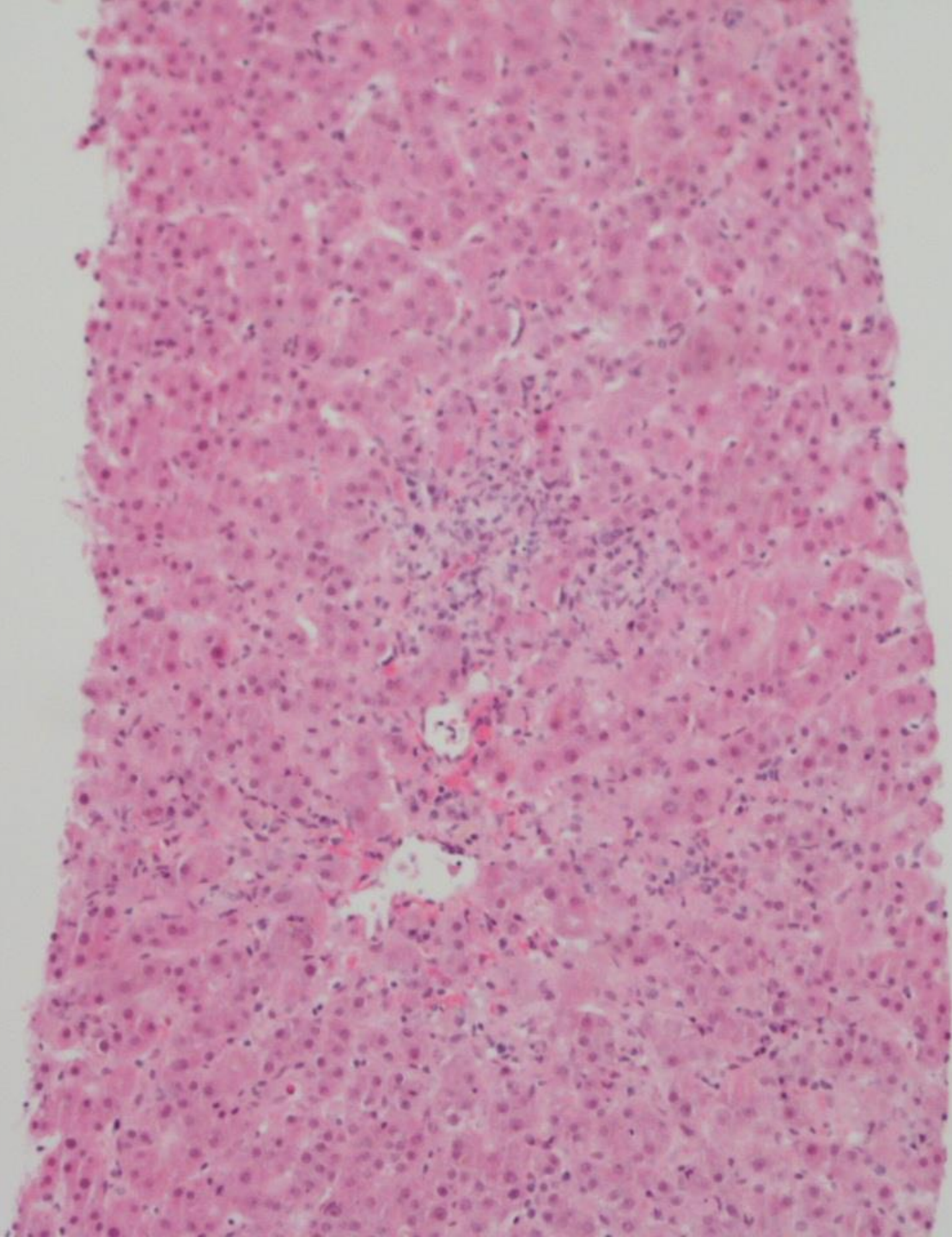




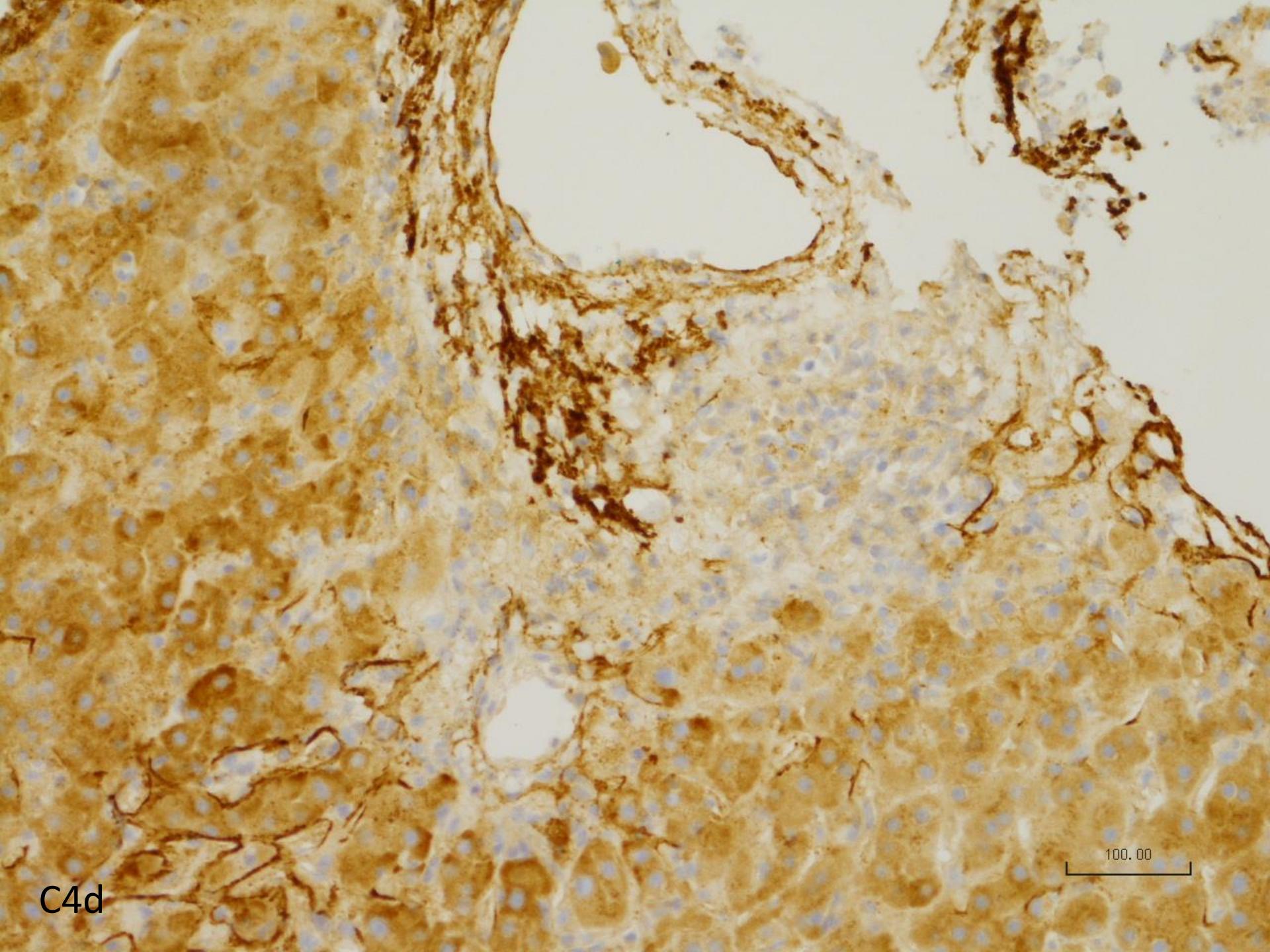
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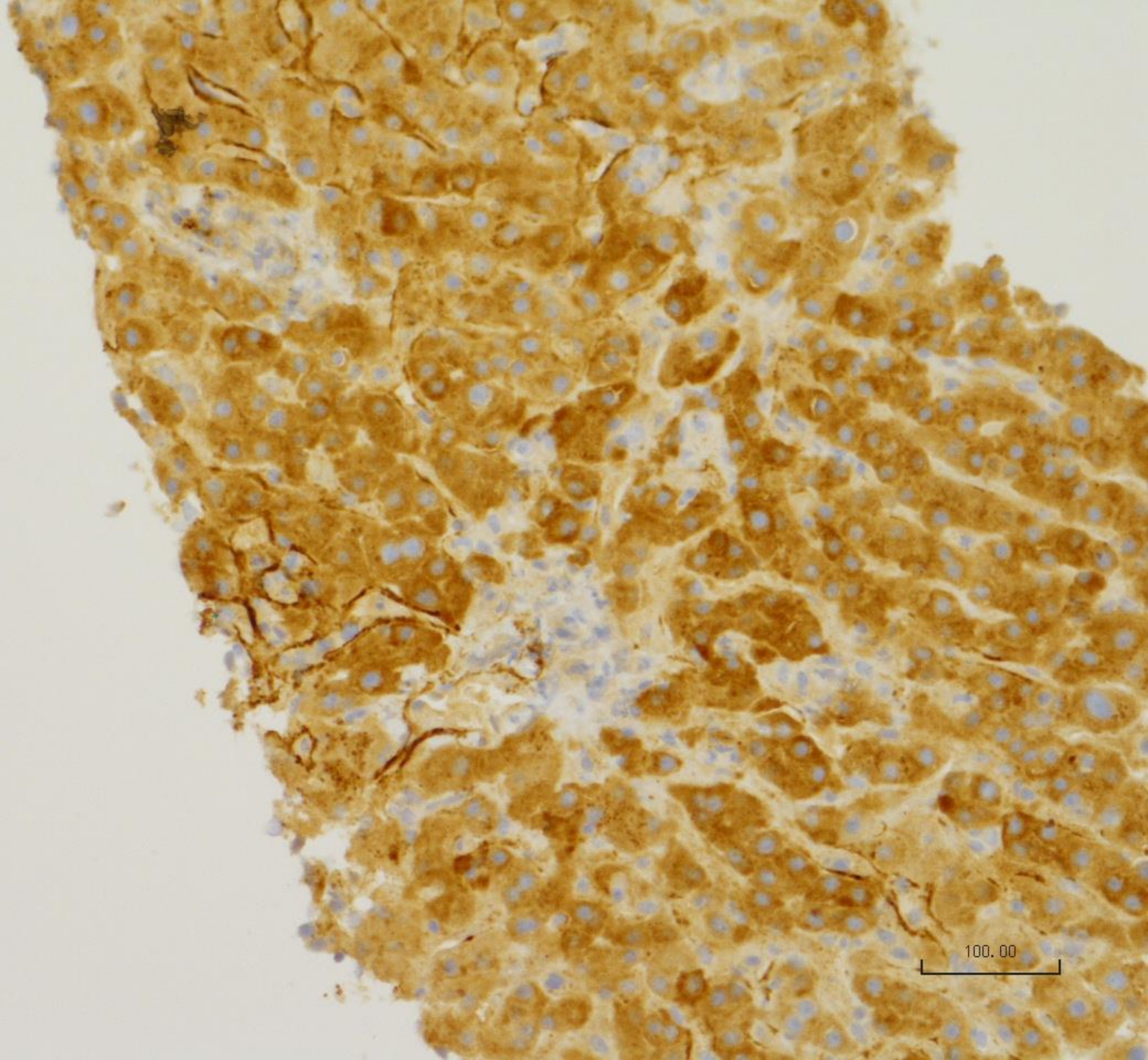
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C4d

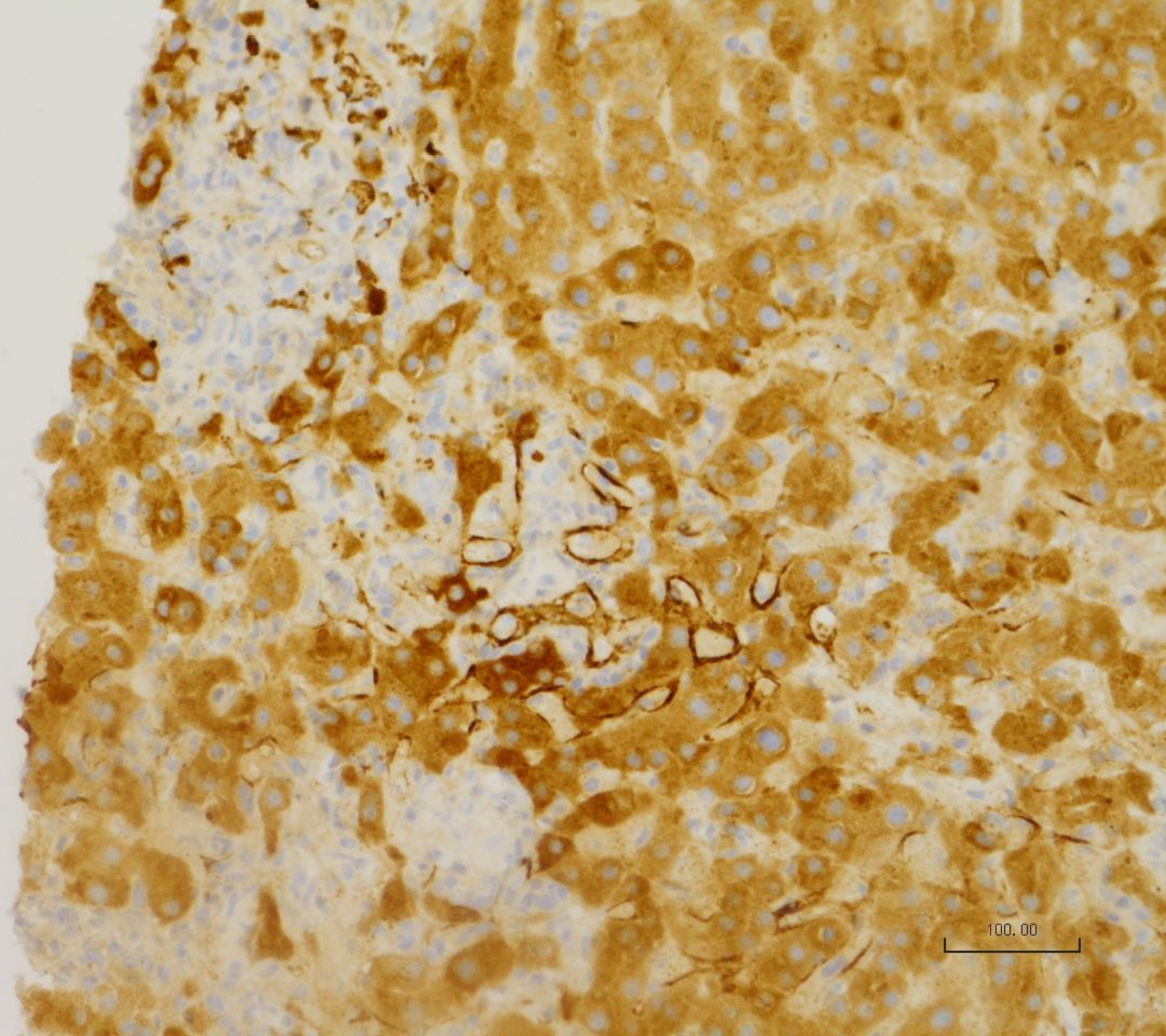
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C4d



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C4d



100.00

- On-going significant moderate hepatitic process within spectrum of atypical TCMR
- ?de novo AIH/rAILD / infection / DILI
- Sinusoidal C4d may be a contributing element of AMR
- Less inflammation to previous biopsy, in particular plasma cells

- Suggest on-going rejection, similar in severity to previous biopsy
- Some features again suggestive of AMR

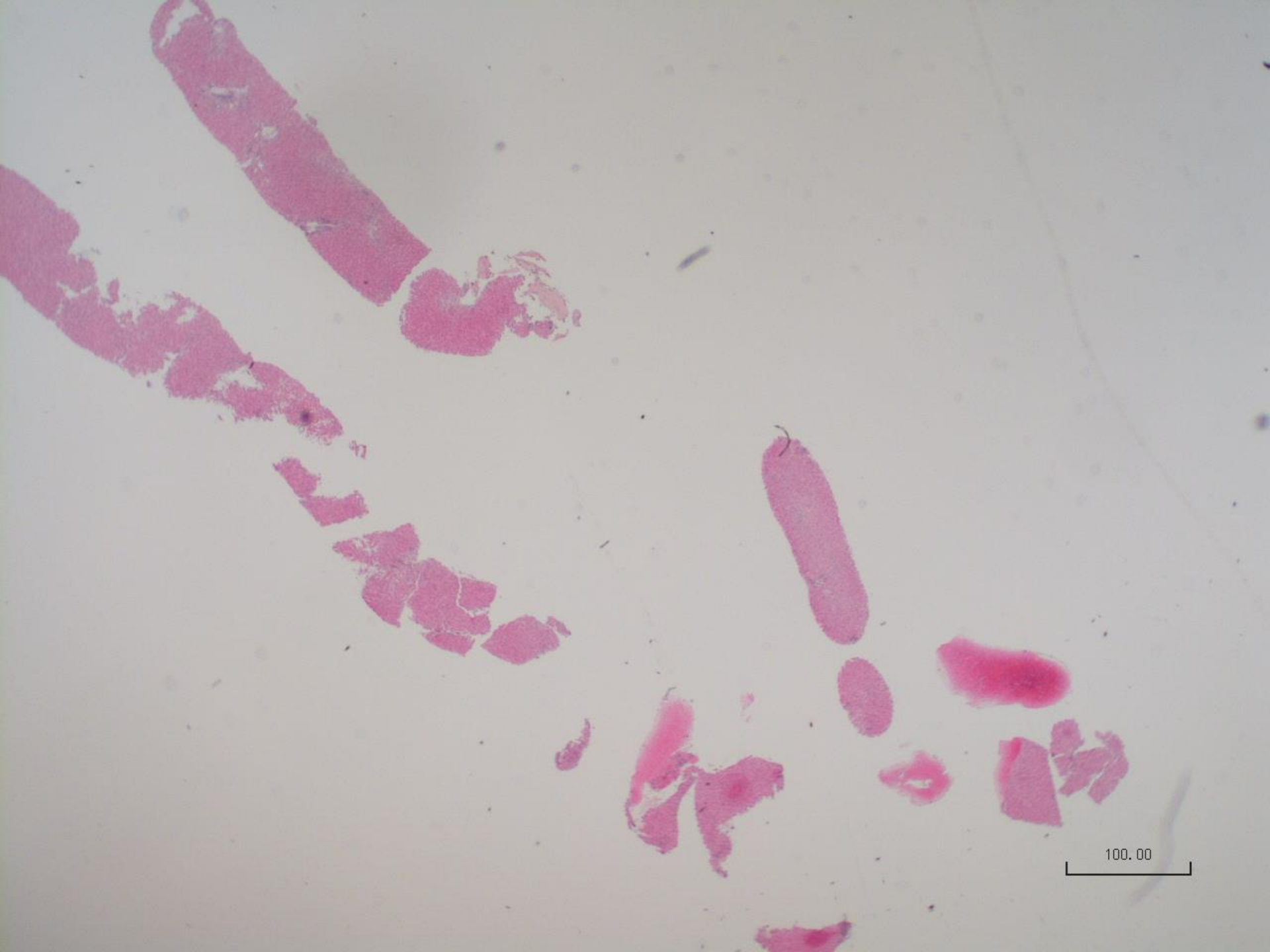
- [Sample from 5/4/17: New DSA Cw4 6328, but no DR1]

- Further pulse with Methylprednisolone
- Post-biopsy switch to MMF, but subsequently suspended due to lymphopenia (not restarted)

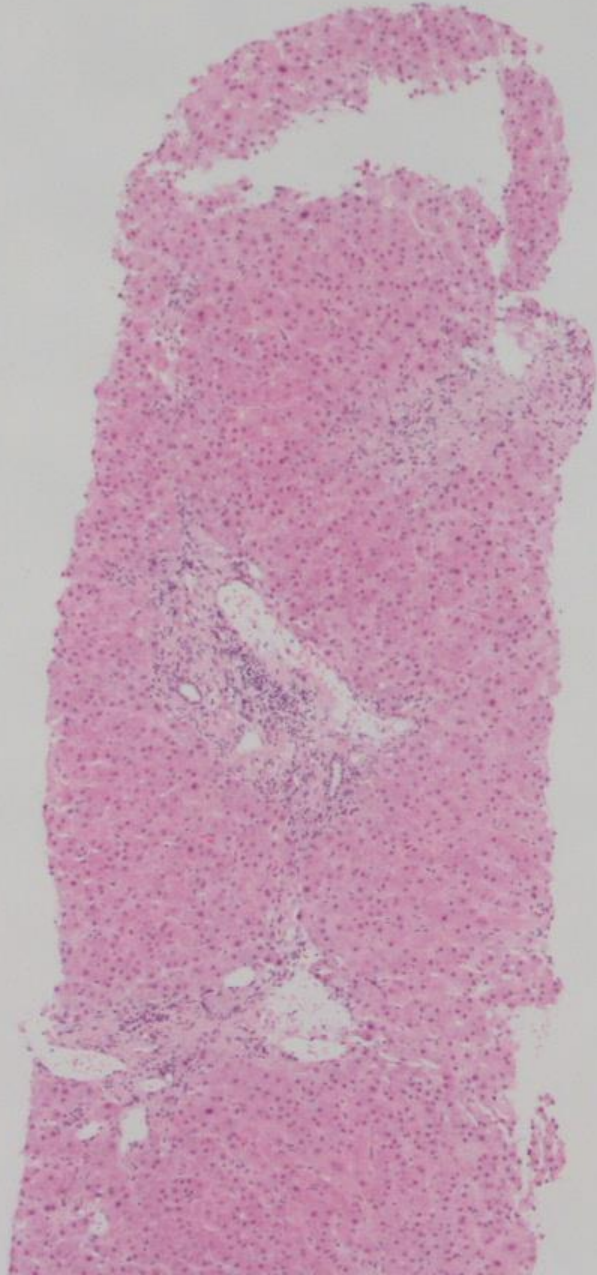
3rd biopsy Thurs 1/06/2017 (day 136)

- Now rising LFTs on background of previous rejection
- Between 29th May and 1st June pulsed with Methylprednisolone
- Other medication included Prednisolone and Tacrolimus only

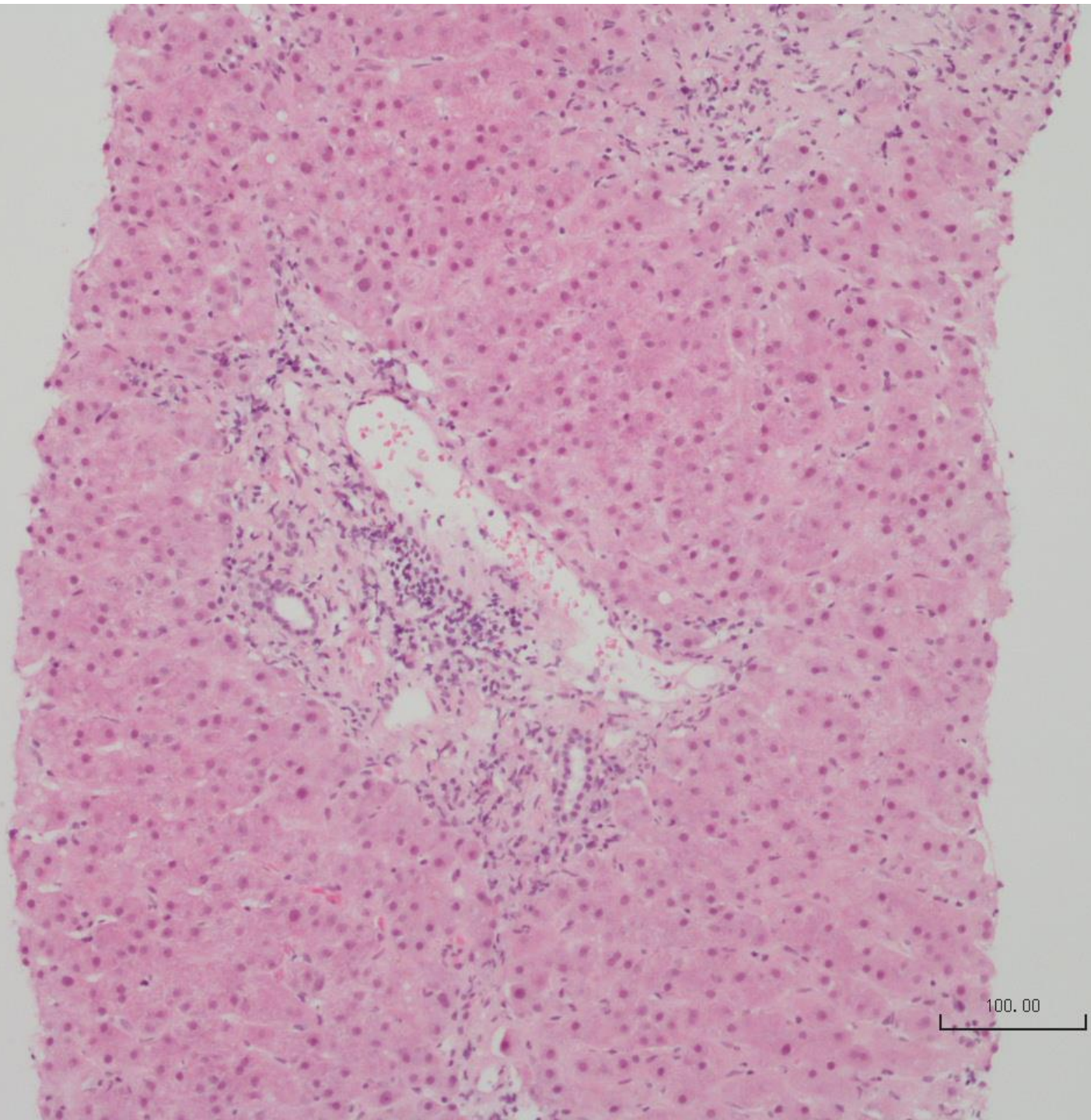
- 29/05/2017:
 - Bilirubin 30
 - ALP 775
 - ALT 261
 - Tacrolimus 0.9



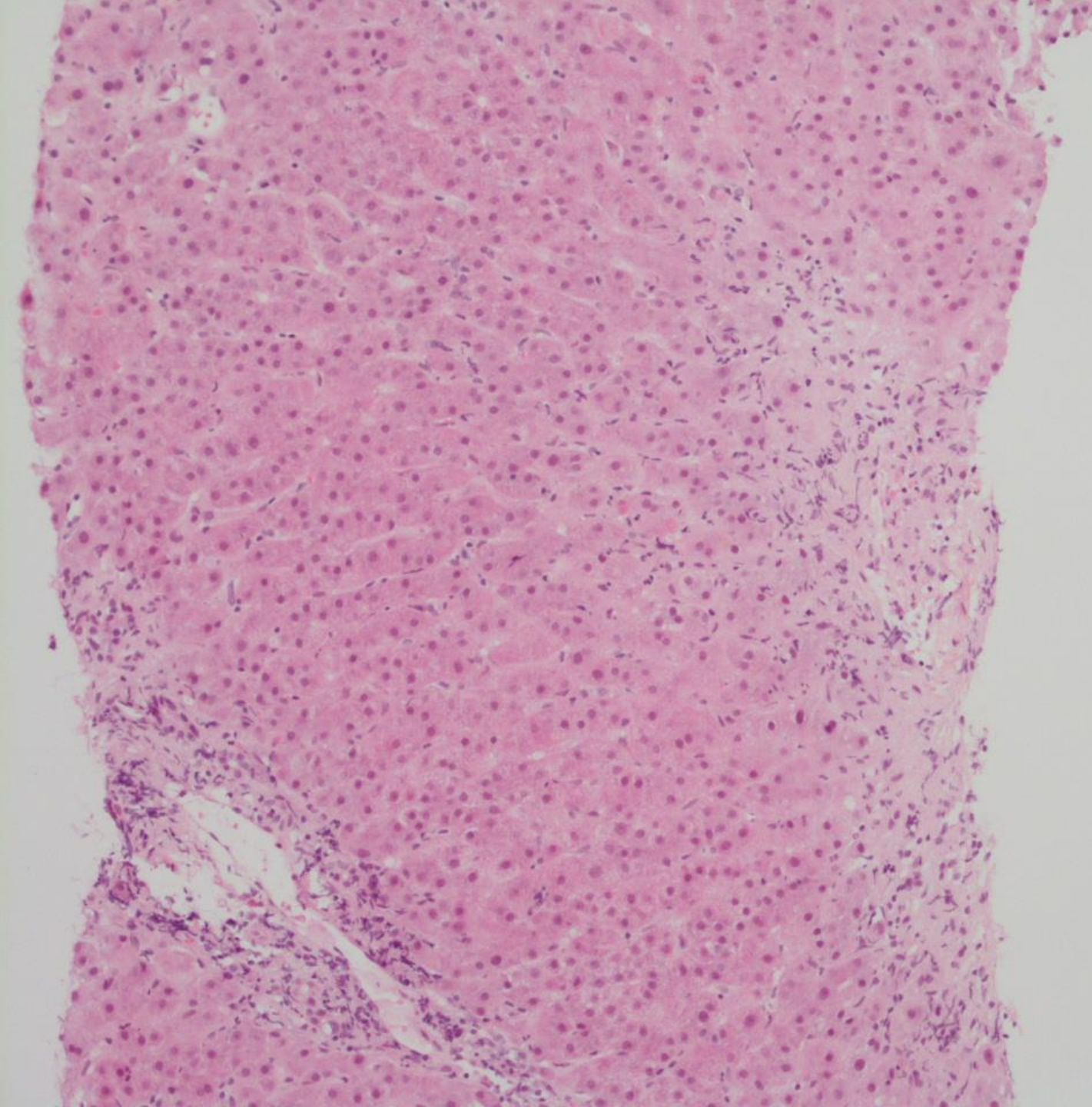
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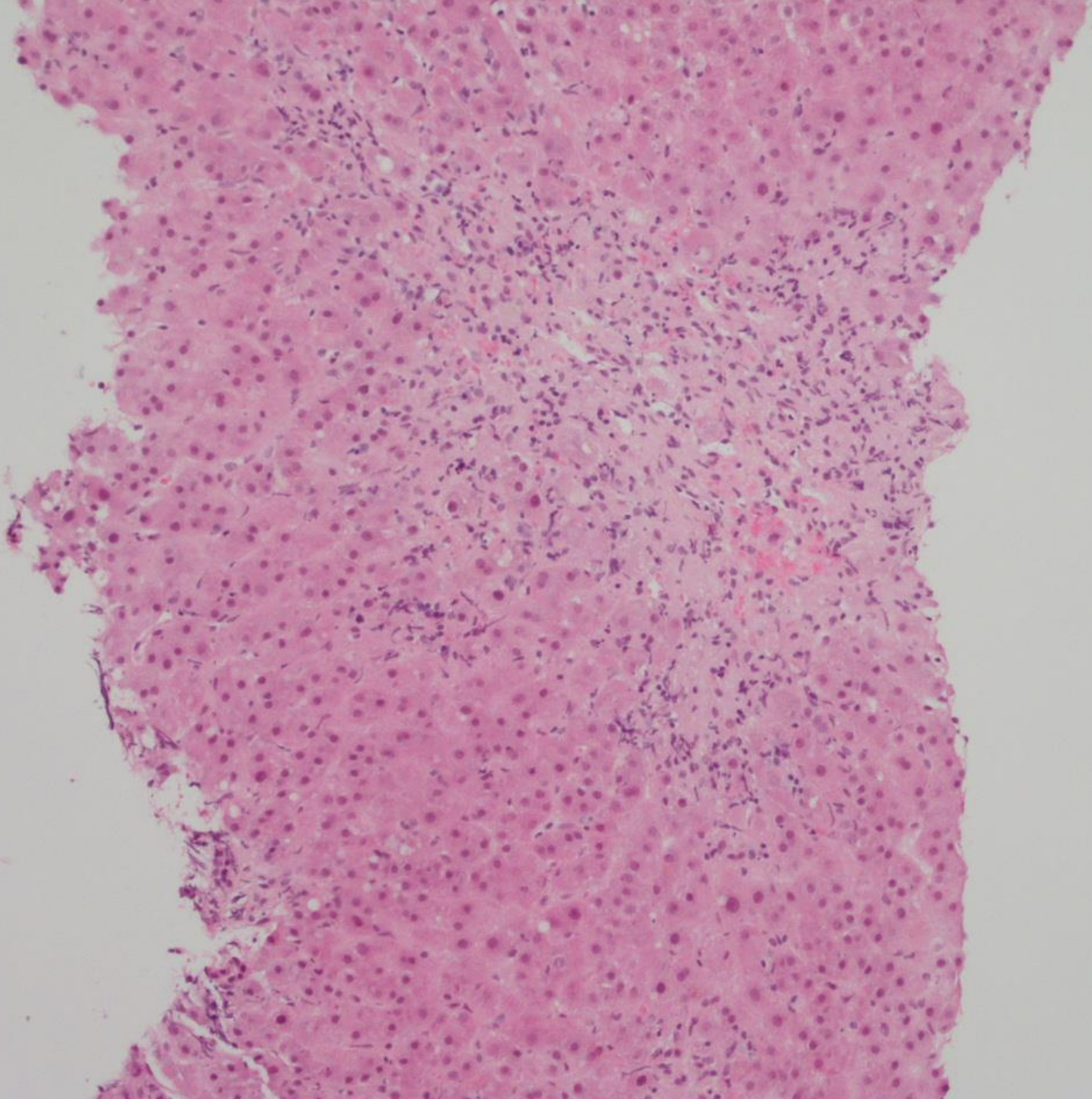
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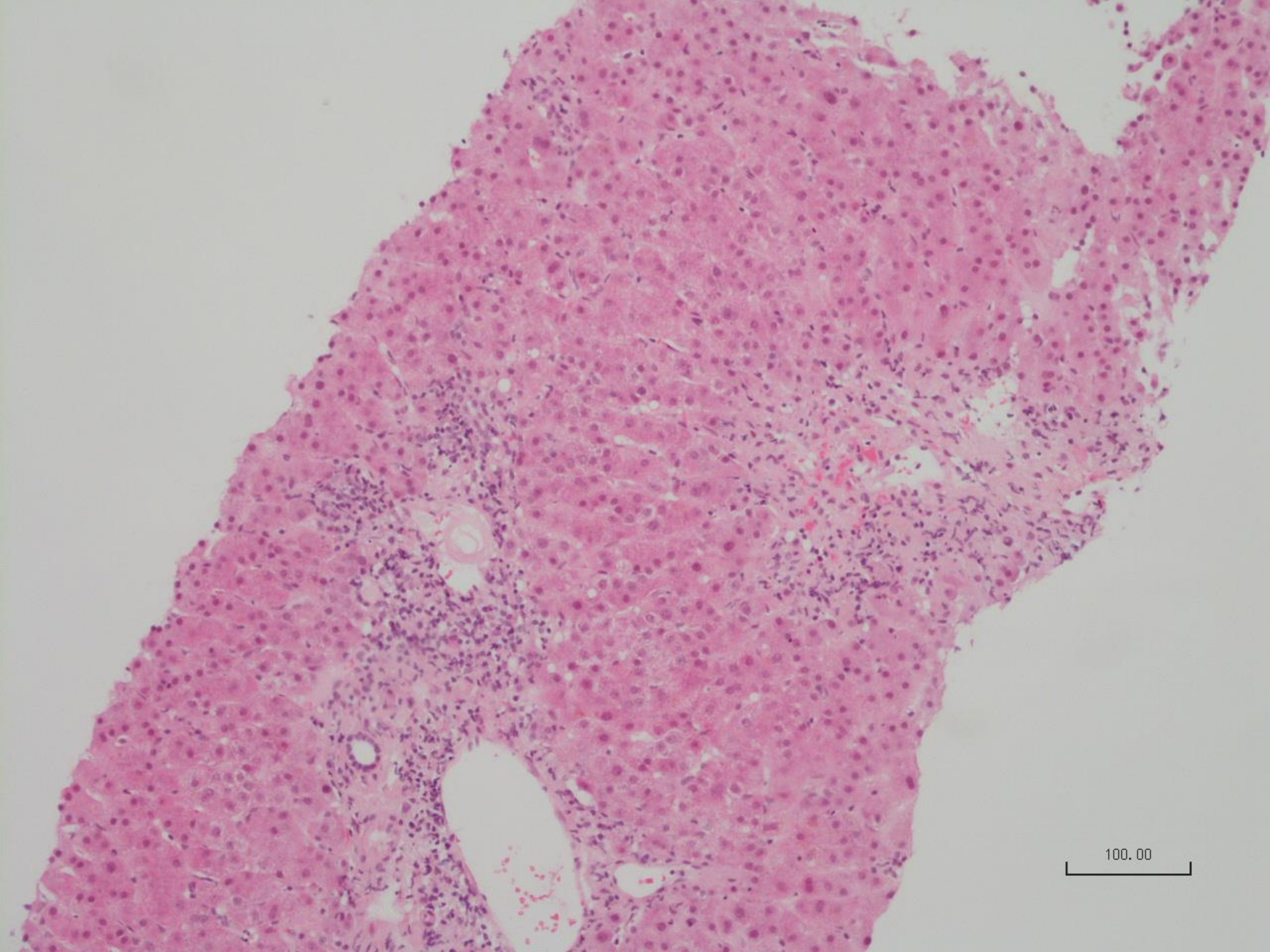
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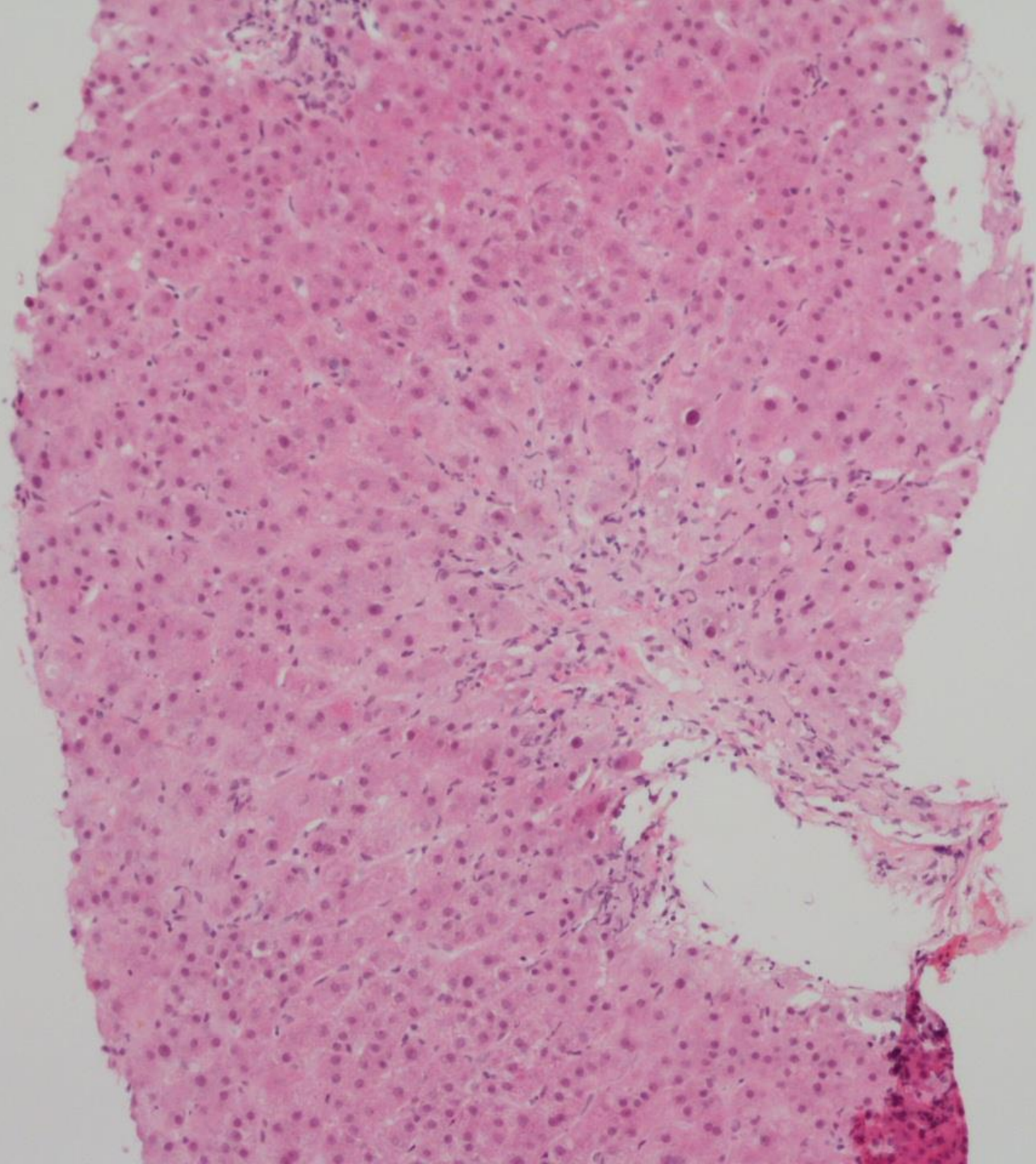
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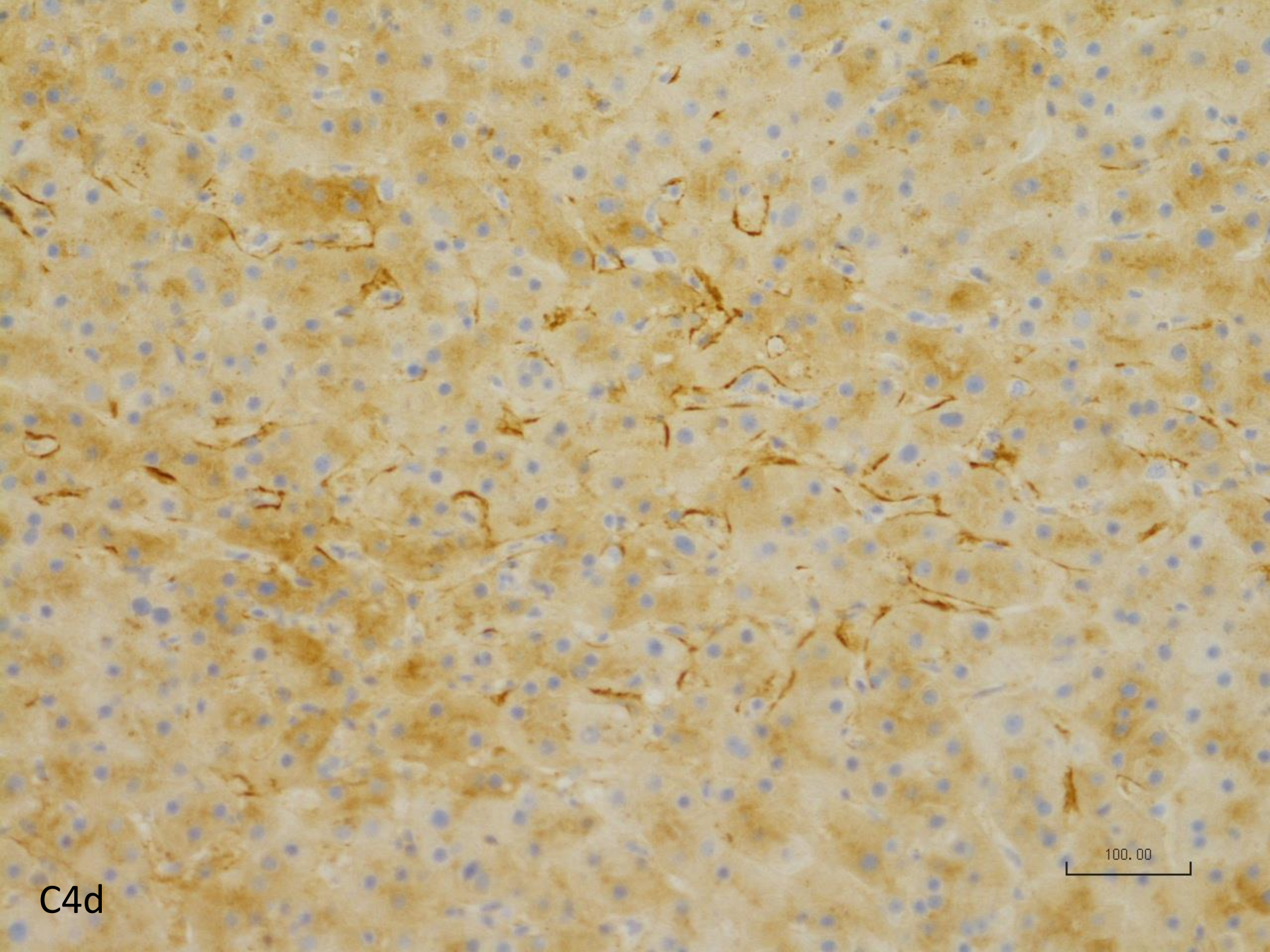
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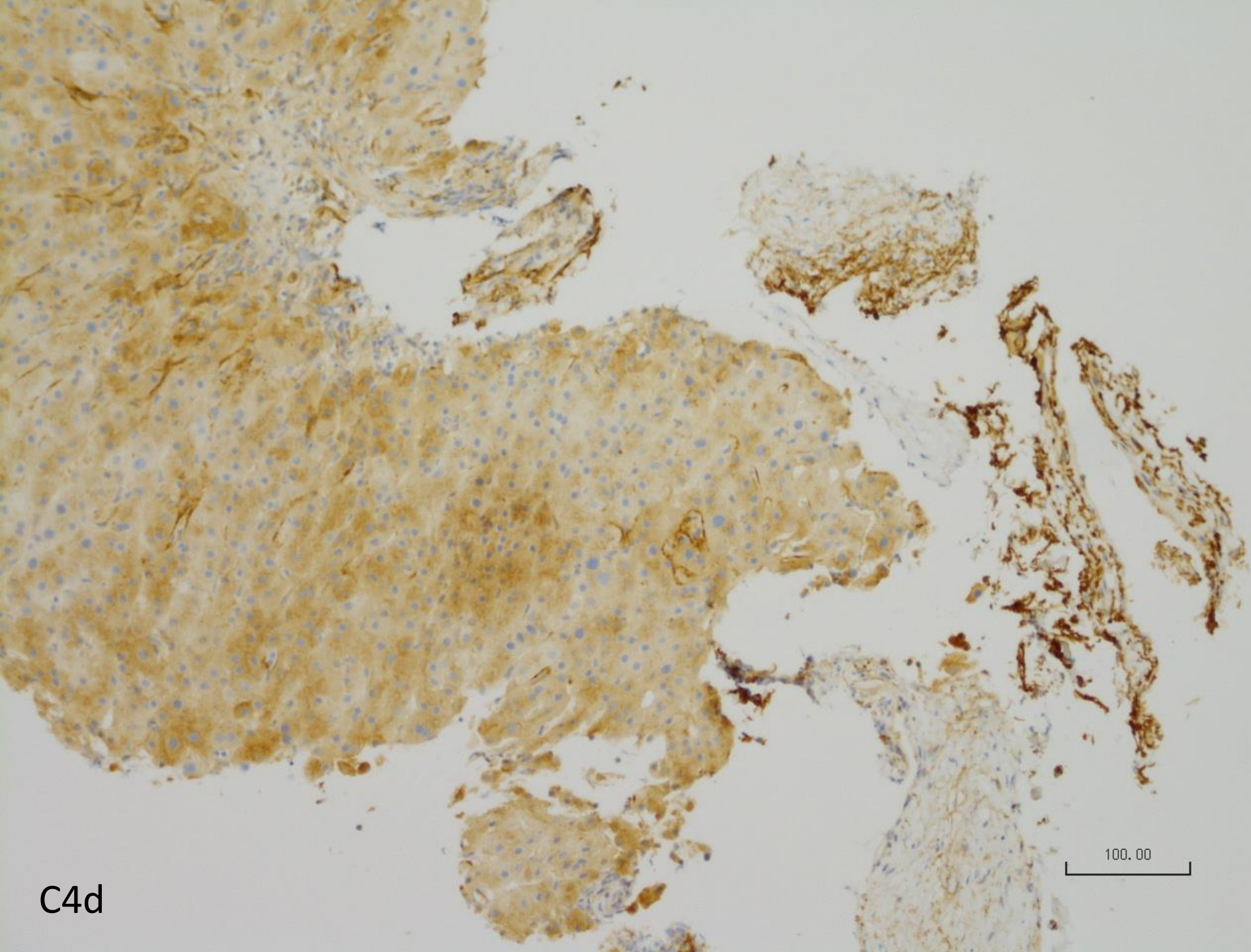


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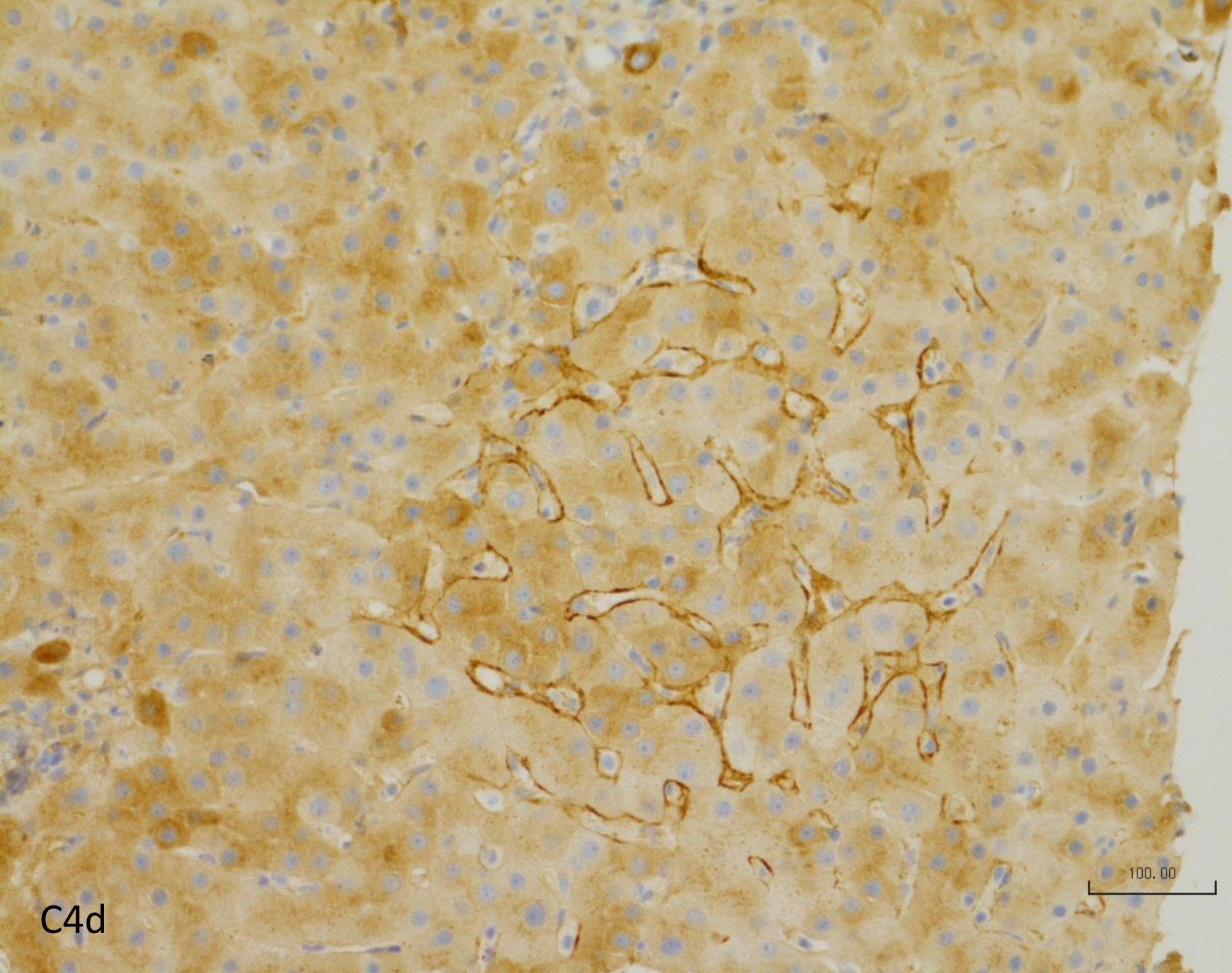
C4d

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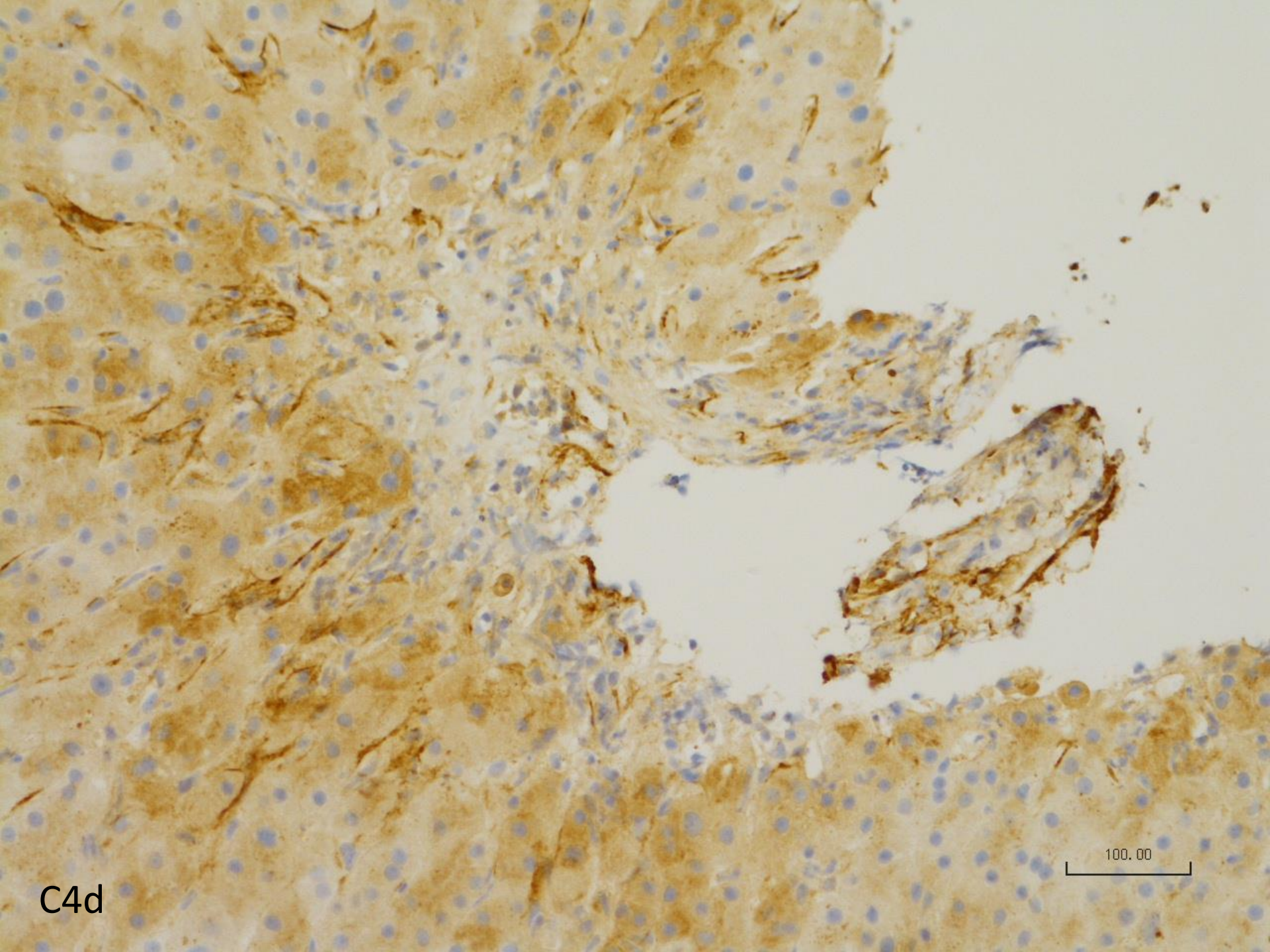
C4d

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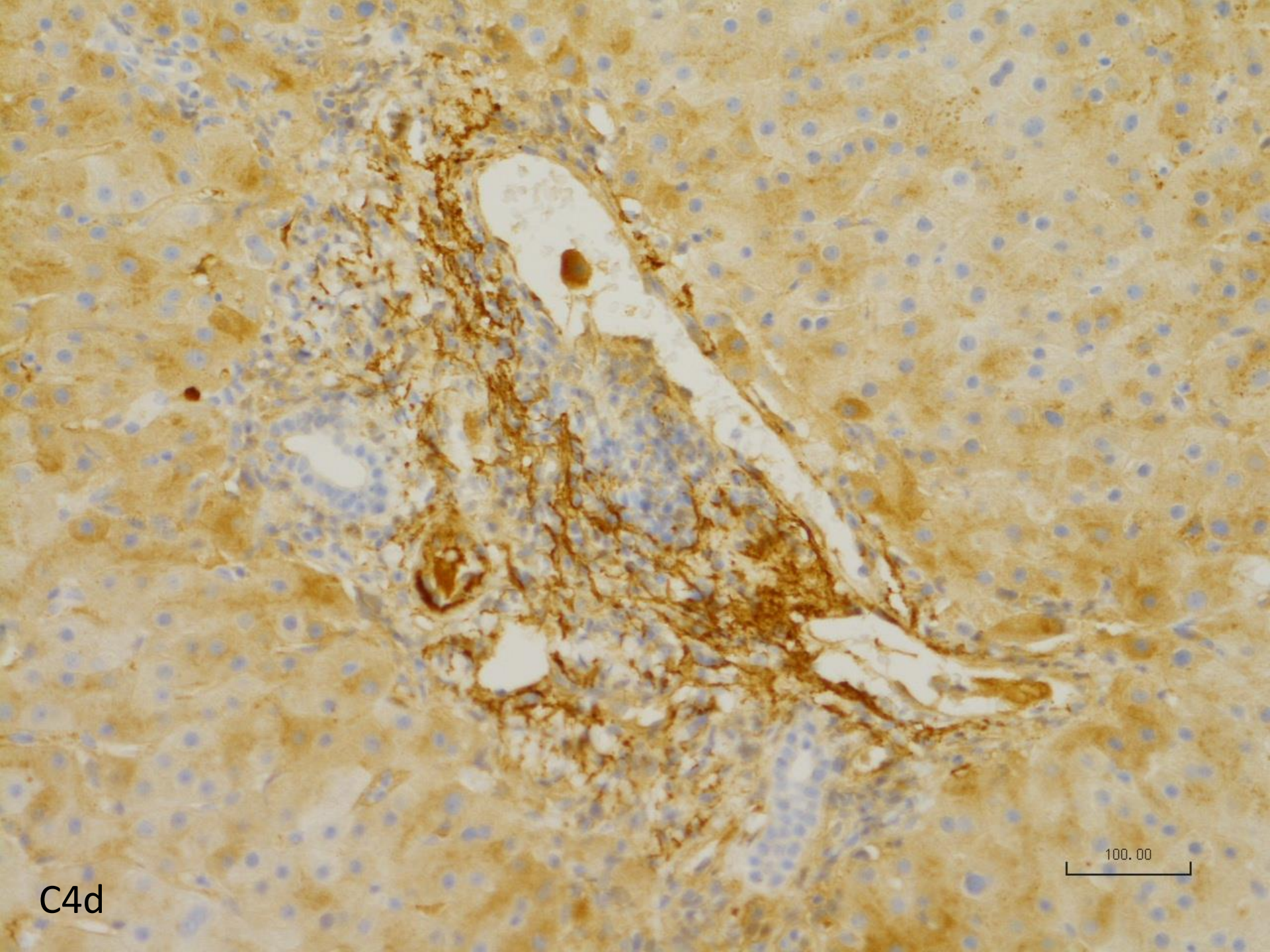
C4d

100.00



C4d

100.00



C4d

100.00

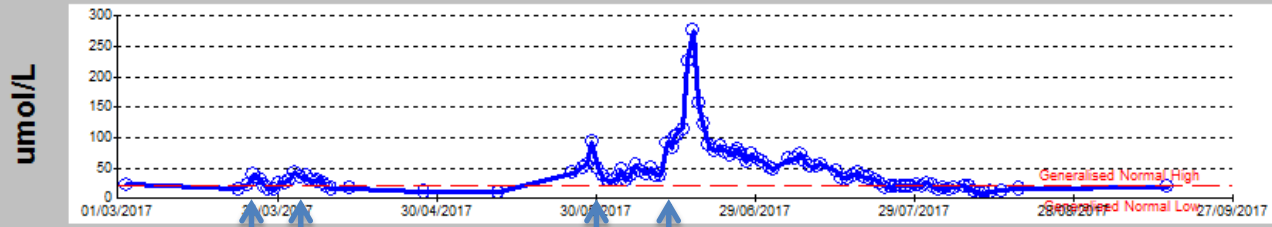
- Hepatitic process with large areas of perivenular necrosis, less inflammation
- could represent an atypical rejection hepatitis
- ?de novo AIH, rAILD

- Support diagnosis of on-going rejection
- Prominent central perivenulitis, best regarded as at least moderate in severity
- Some features again favour diagnosis of AMR

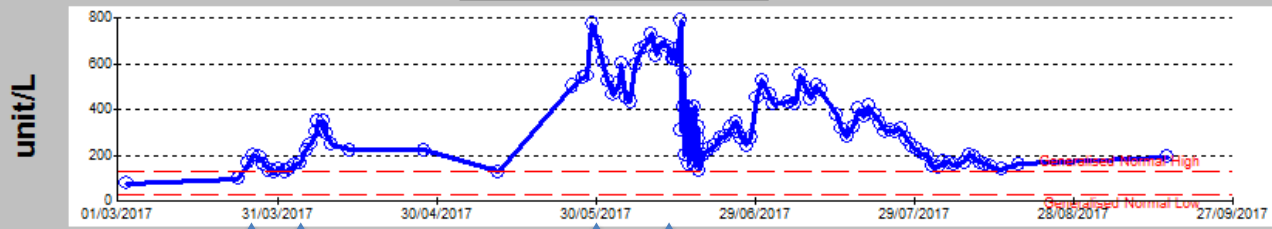
- [Sample 30/5/17: Cw4 DSA 7741, still no DR1]

- Following this biopsy she had 4 doses of ATG between 3rd -12th June (test dose on 2nd June)
- This included 'pre-med' of 100mg hydrocortisone with each infusion
- Tacrolimus was withheld whilst ATG was being given
- LFTs spiked so it was restarted on 14th June – patient took first dose on 15th June
- Plasmapheresis started 14/6/2017. Further biopsy arranged.

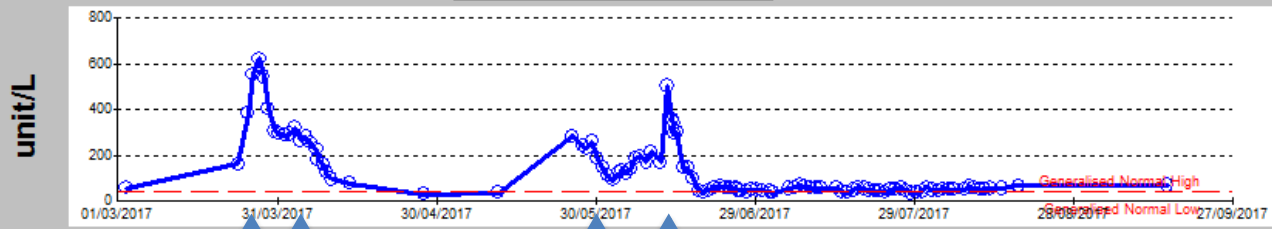
Bilirubin



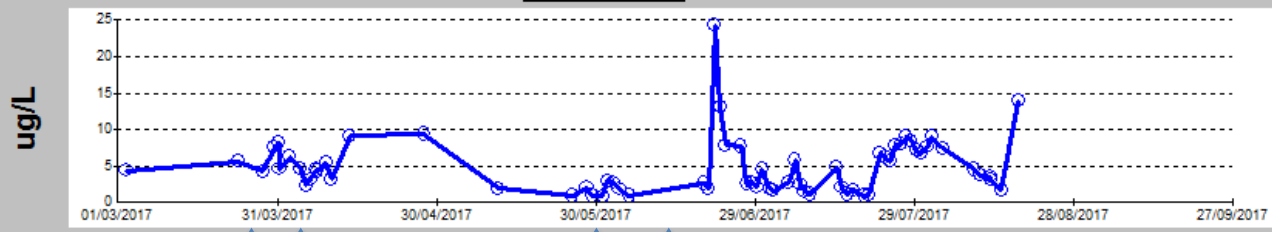
Alkaline Phosphatase



Alanine Transaminase



Tacrolimus

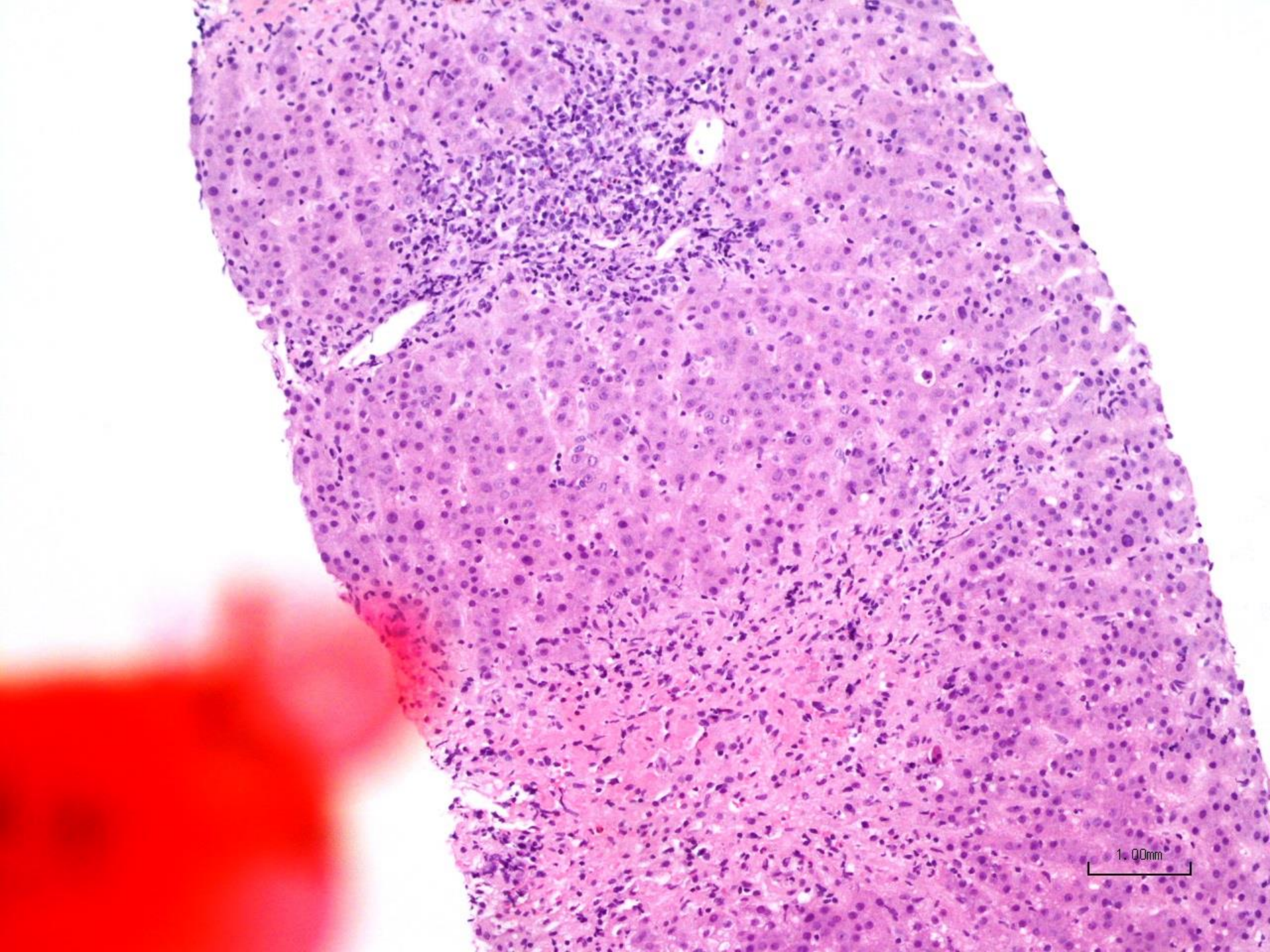


4th biopsy Thurs 15/06/2017 (150 days)

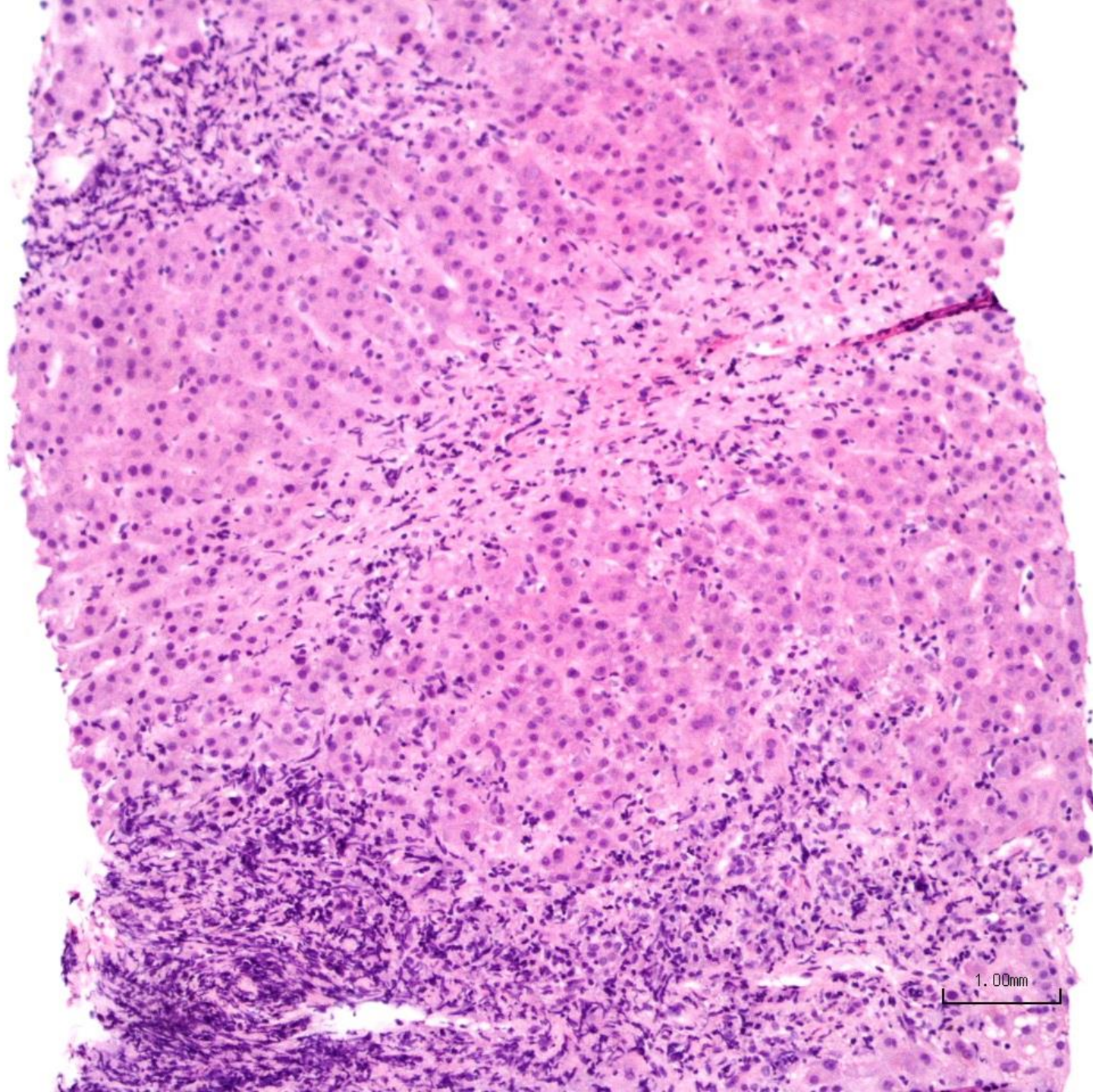
- Had ATG x4 and plasmapheresis x2 at this stage, ATG treatment followed by rapid rise of LFTs
- Tacrolimus had just been restarted and Prednisolone was ongoing
- LFTs continue to rise, imaging of vasculature not abnormal, virus serology sent off (pending Hep E)
- 14/06/17:
 - Bilirubin 104
 - ALP 619
 - ALT 301
 - Tacrolimus less than 0.8
 - **CMV DNA $<2 \times 10^3$, EBV DNA 9.4×10^3**



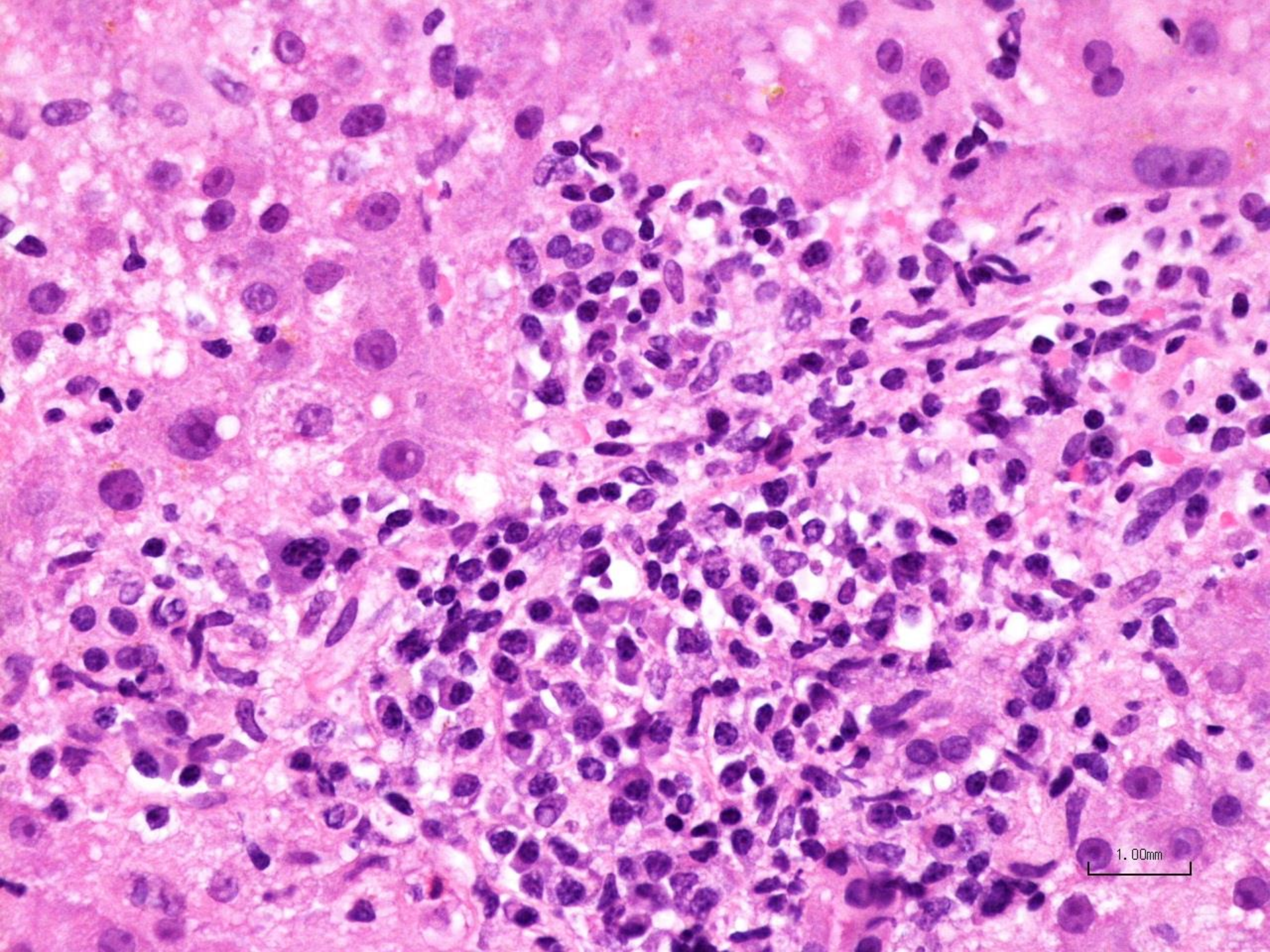
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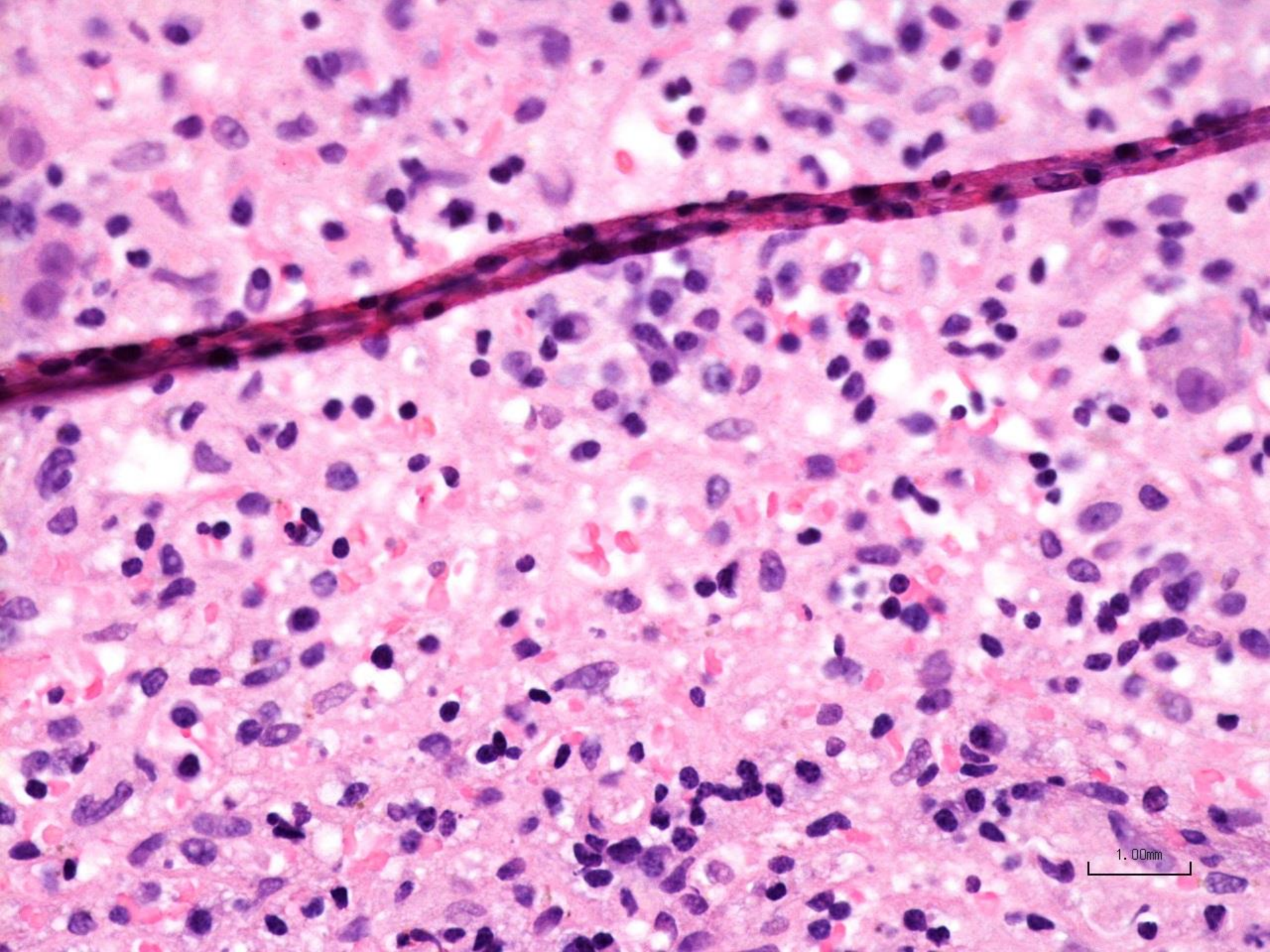


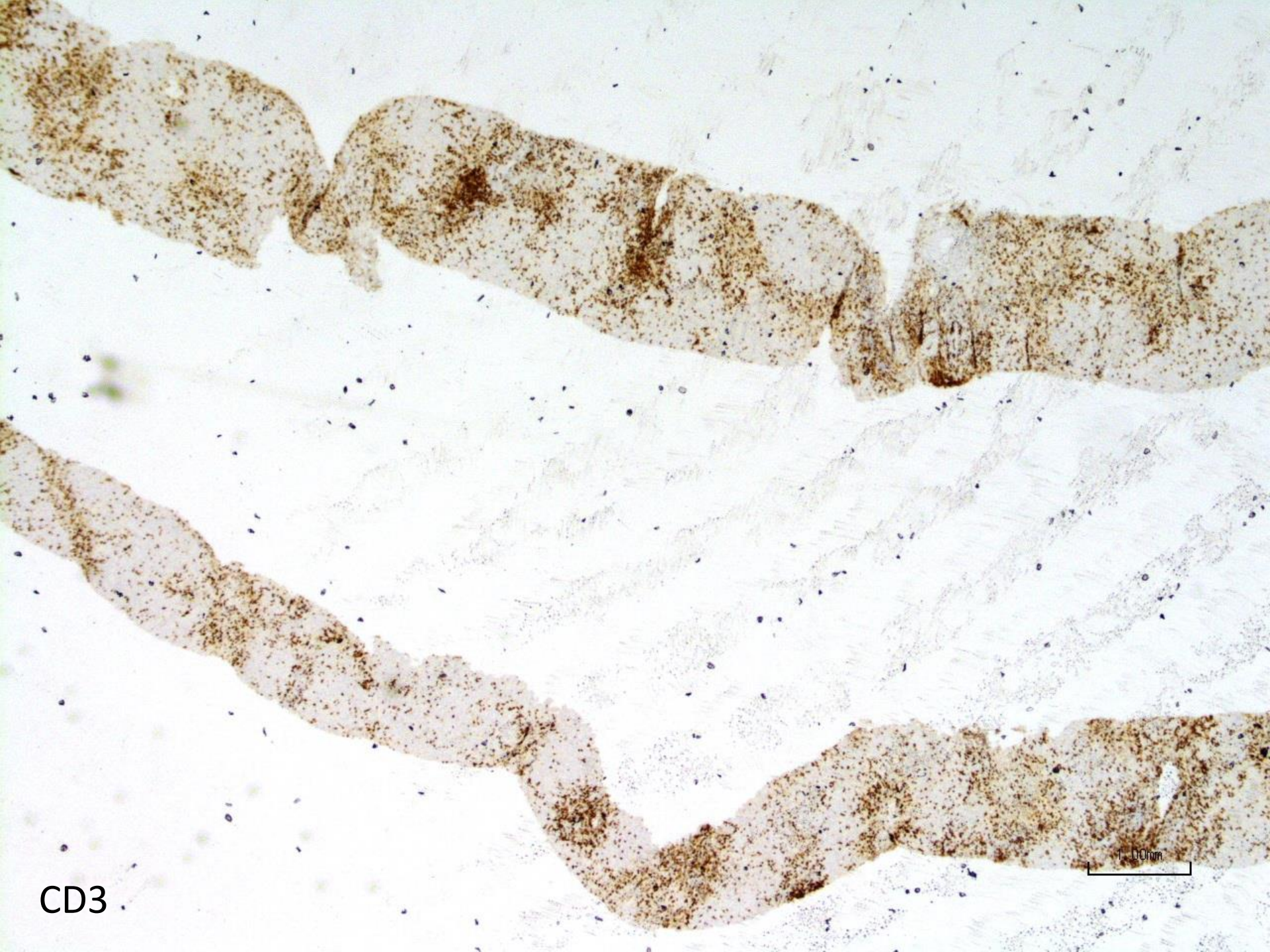
1.00mm



1.00mm







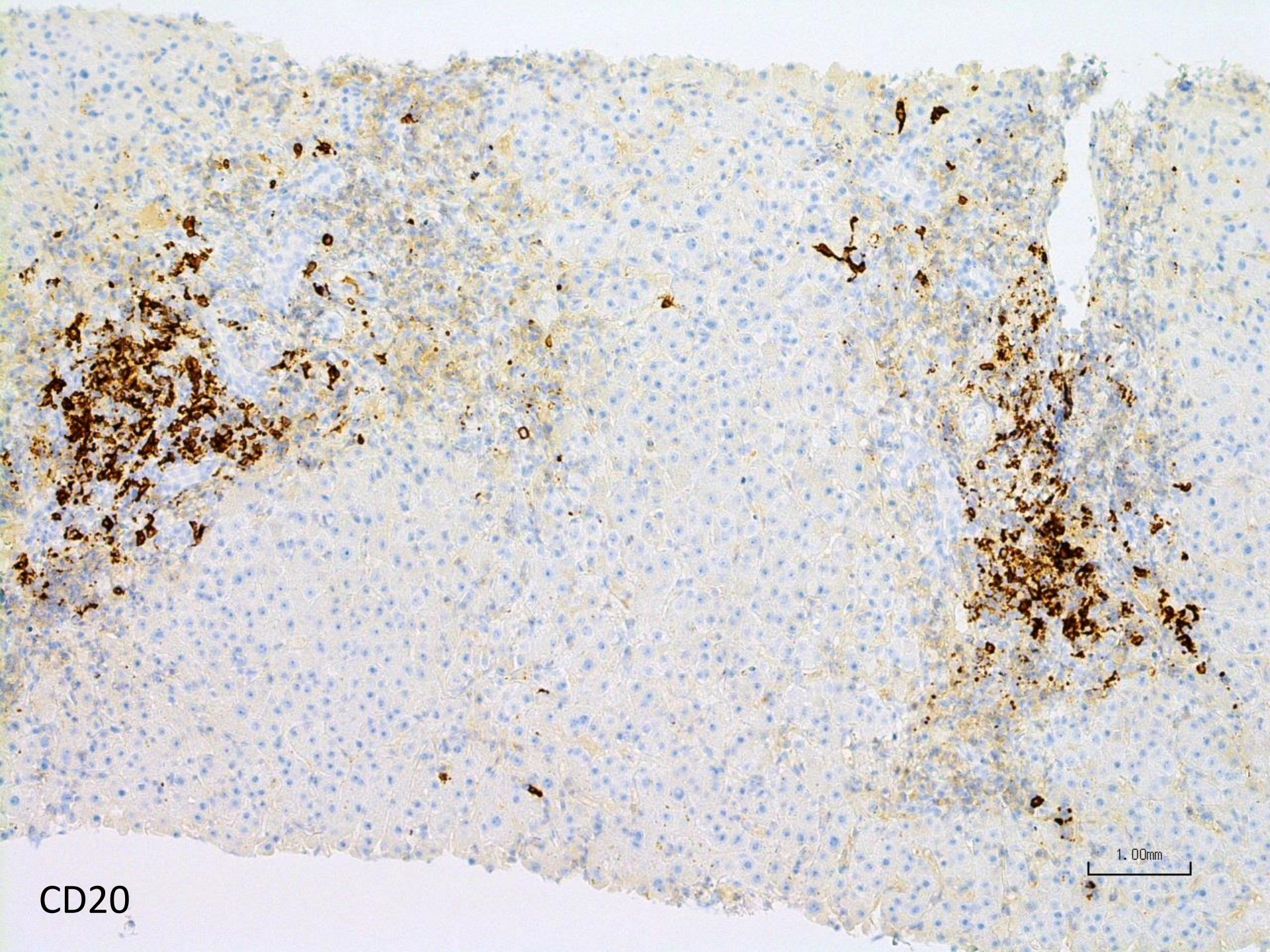
CD3

1.00mm



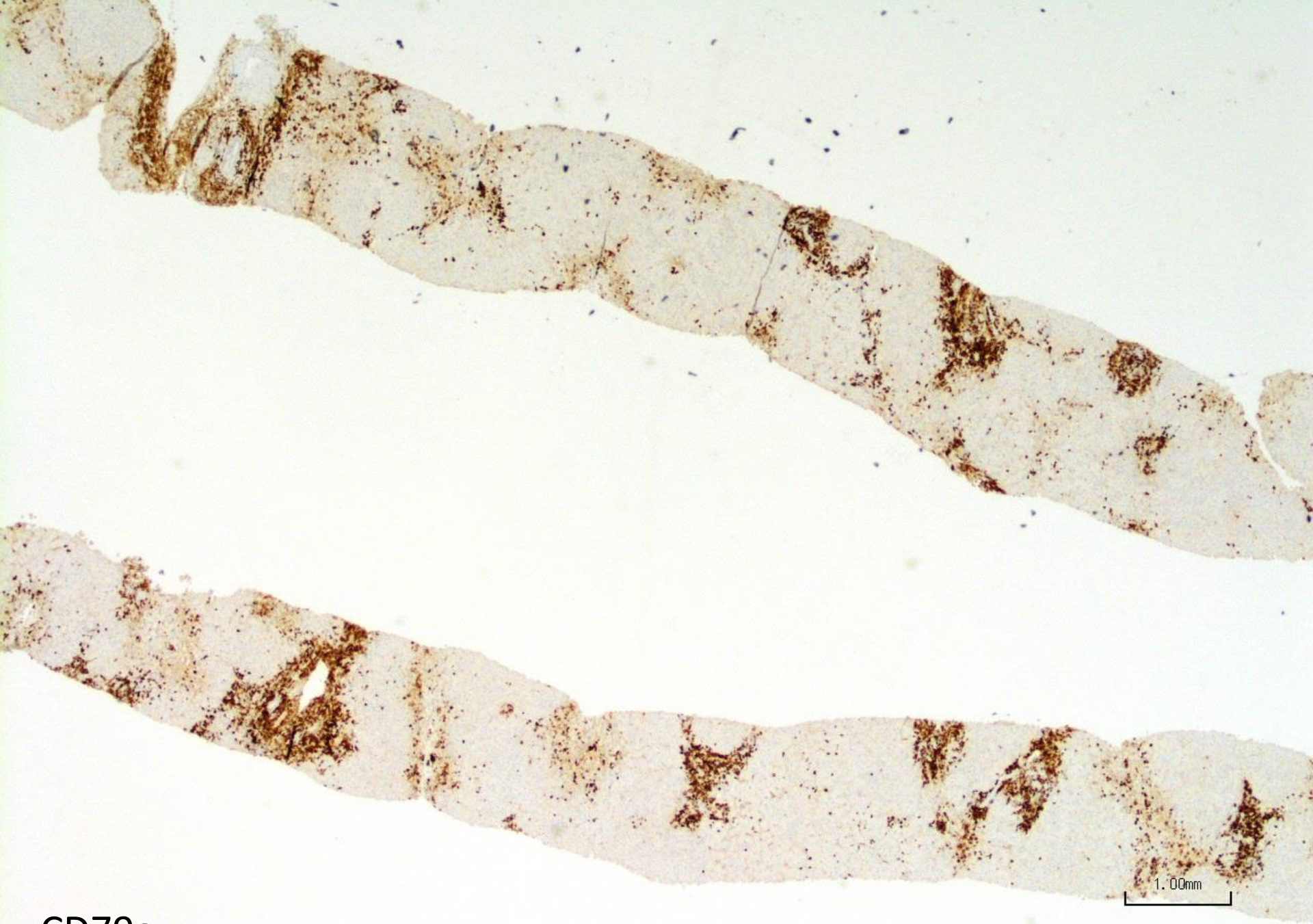
CD20

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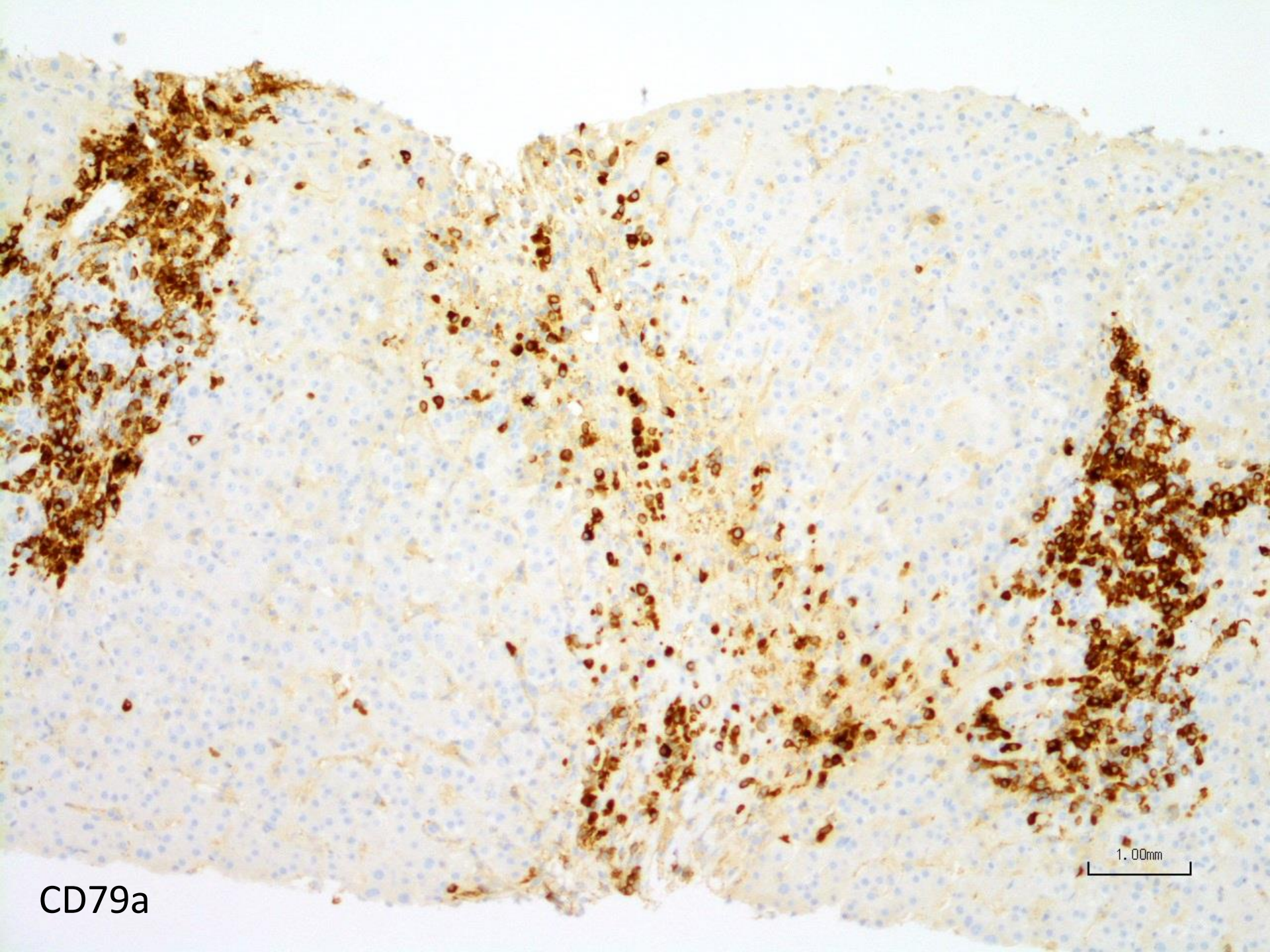
CD20

1.00mm



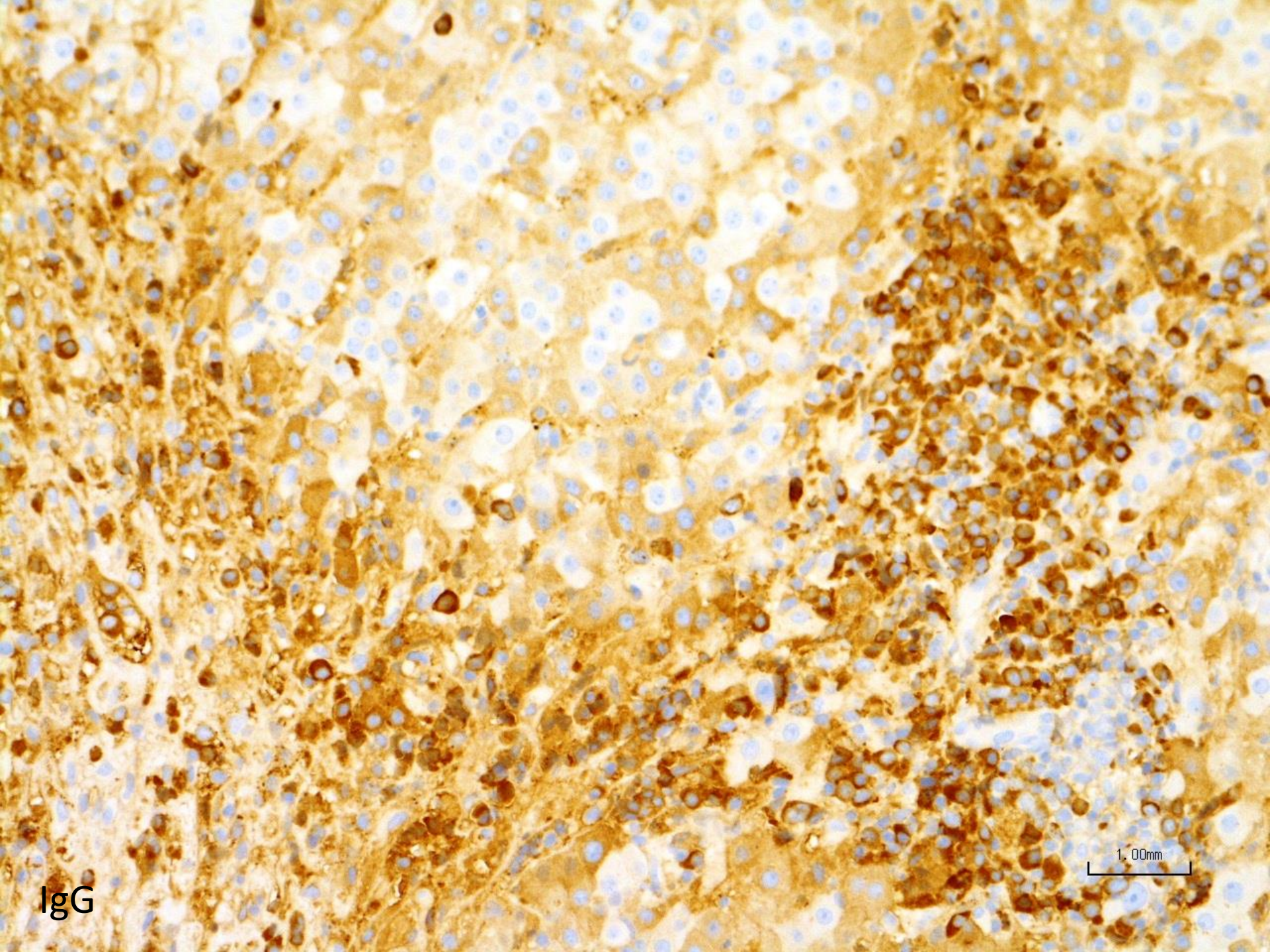
CD79a

1.00mm



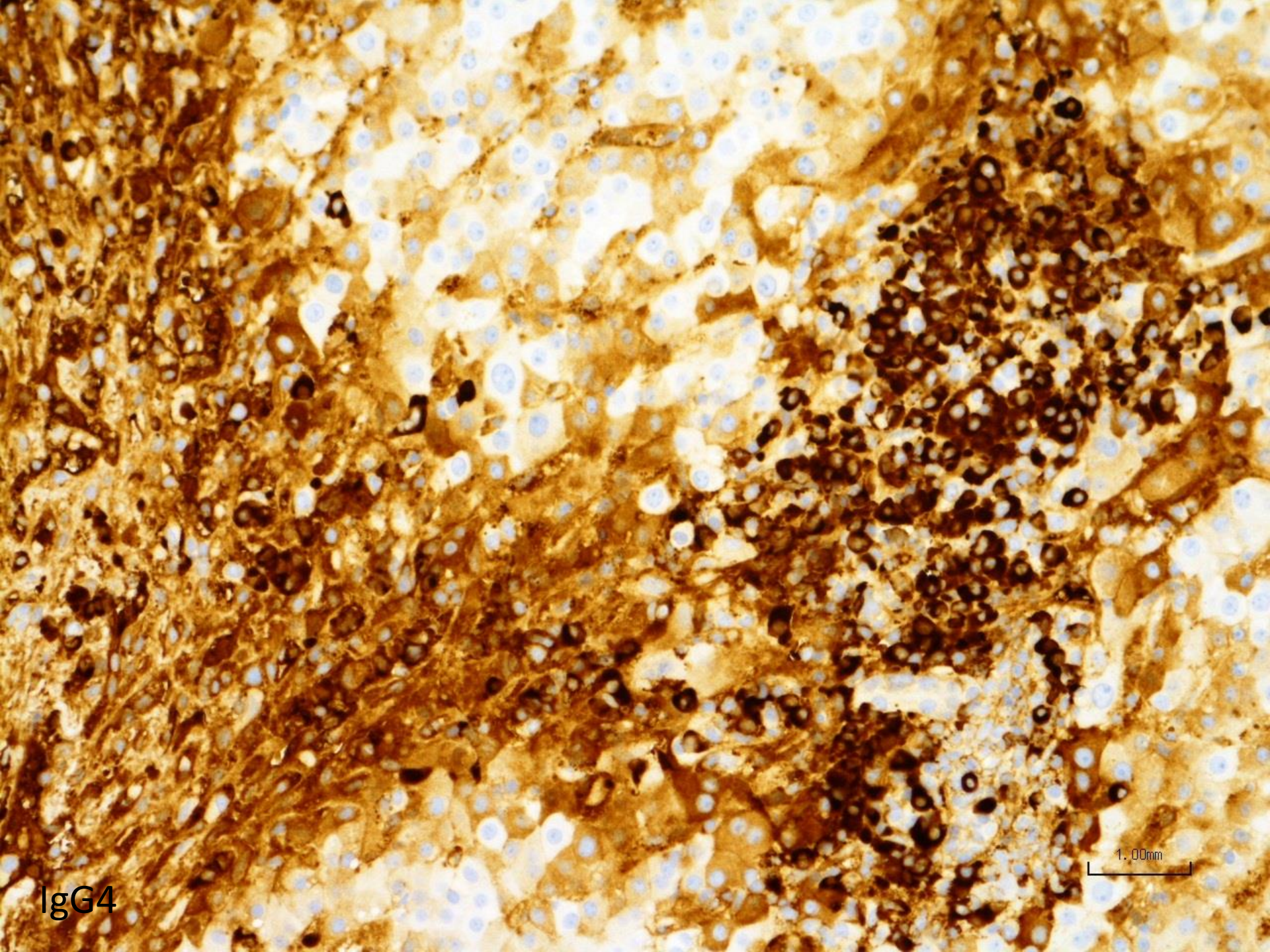
CD79a

1.00mm



IgG

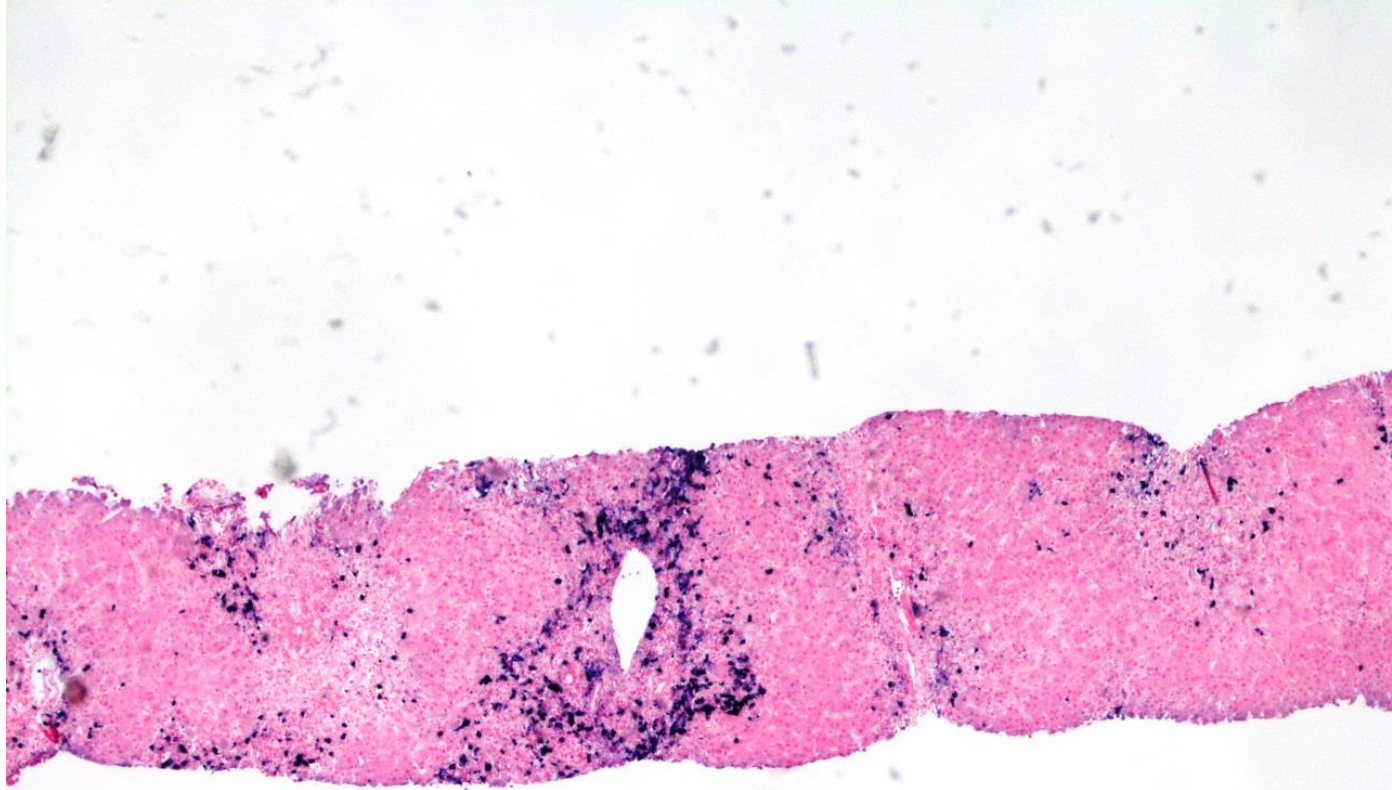
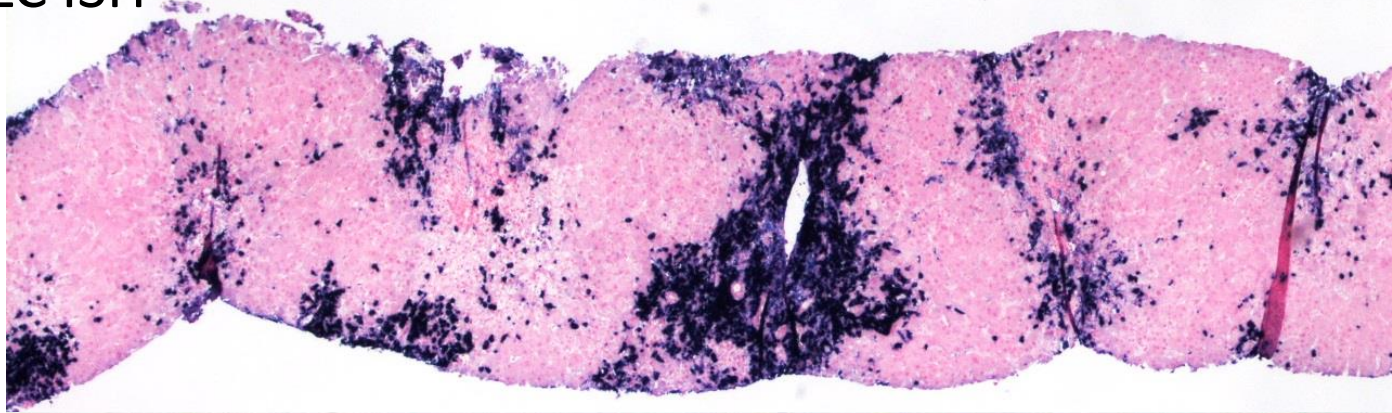
1.00mm



IgG4

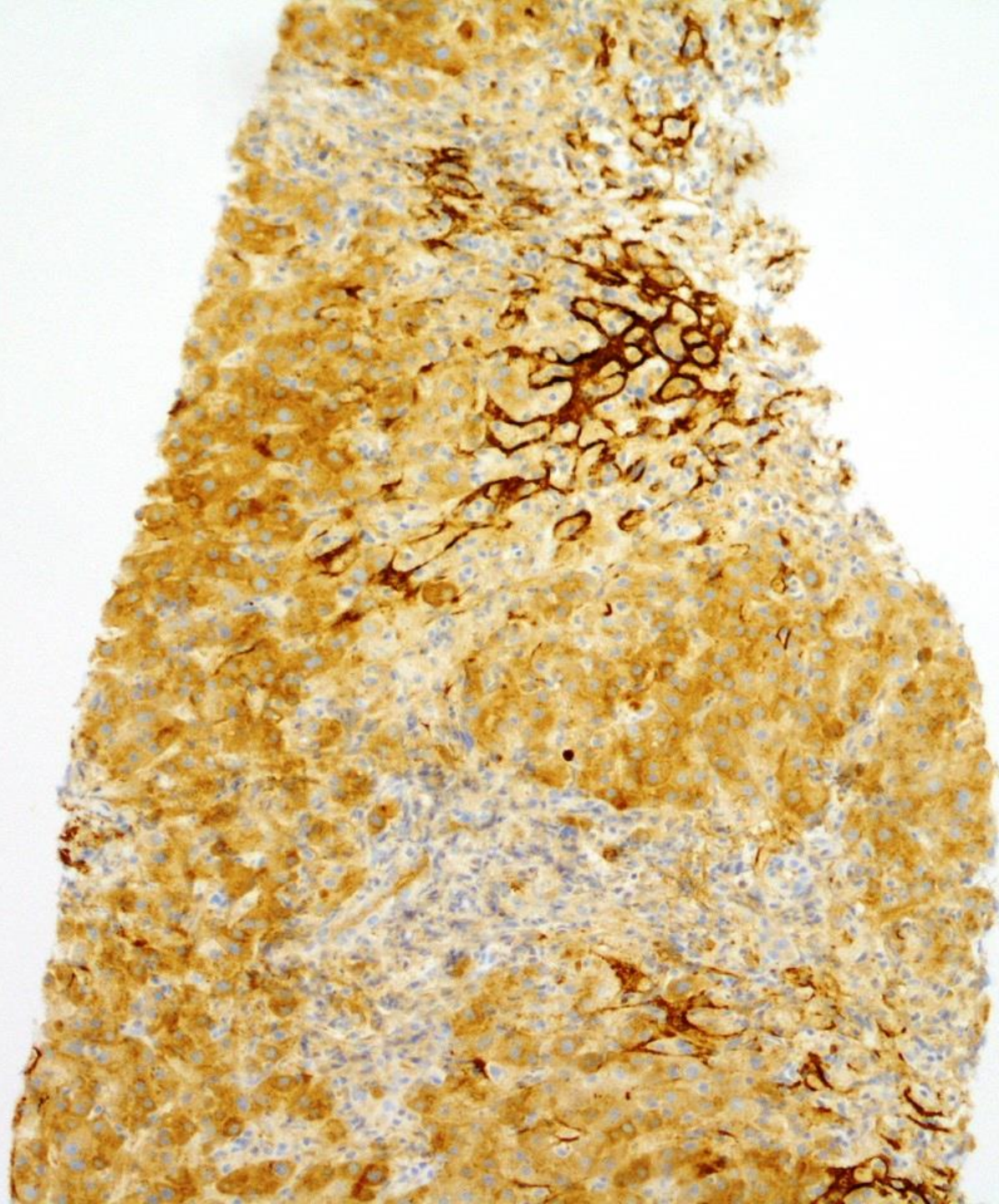
1.00mm

Kappa LC ISH



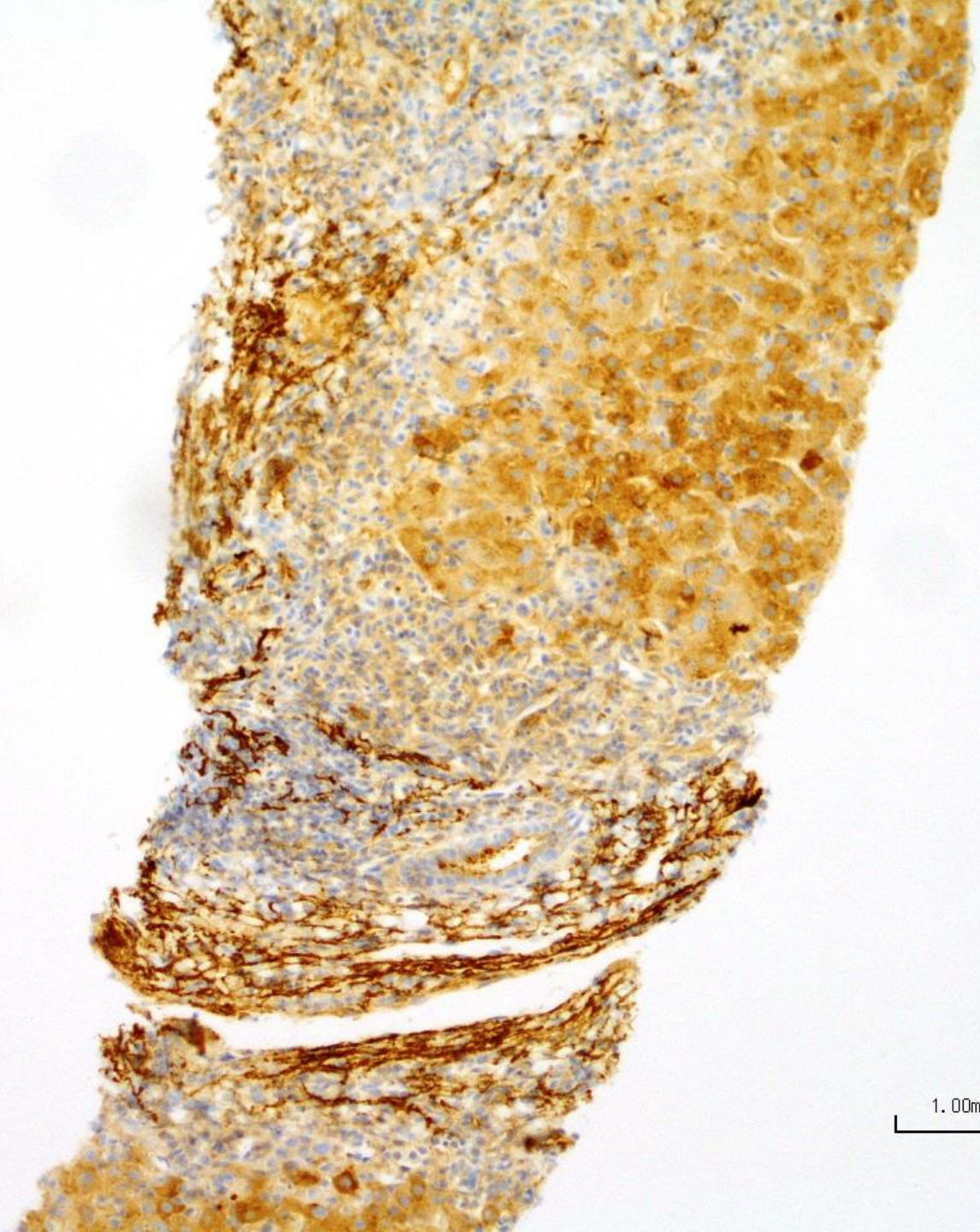
Lambda LC ISH

C4d

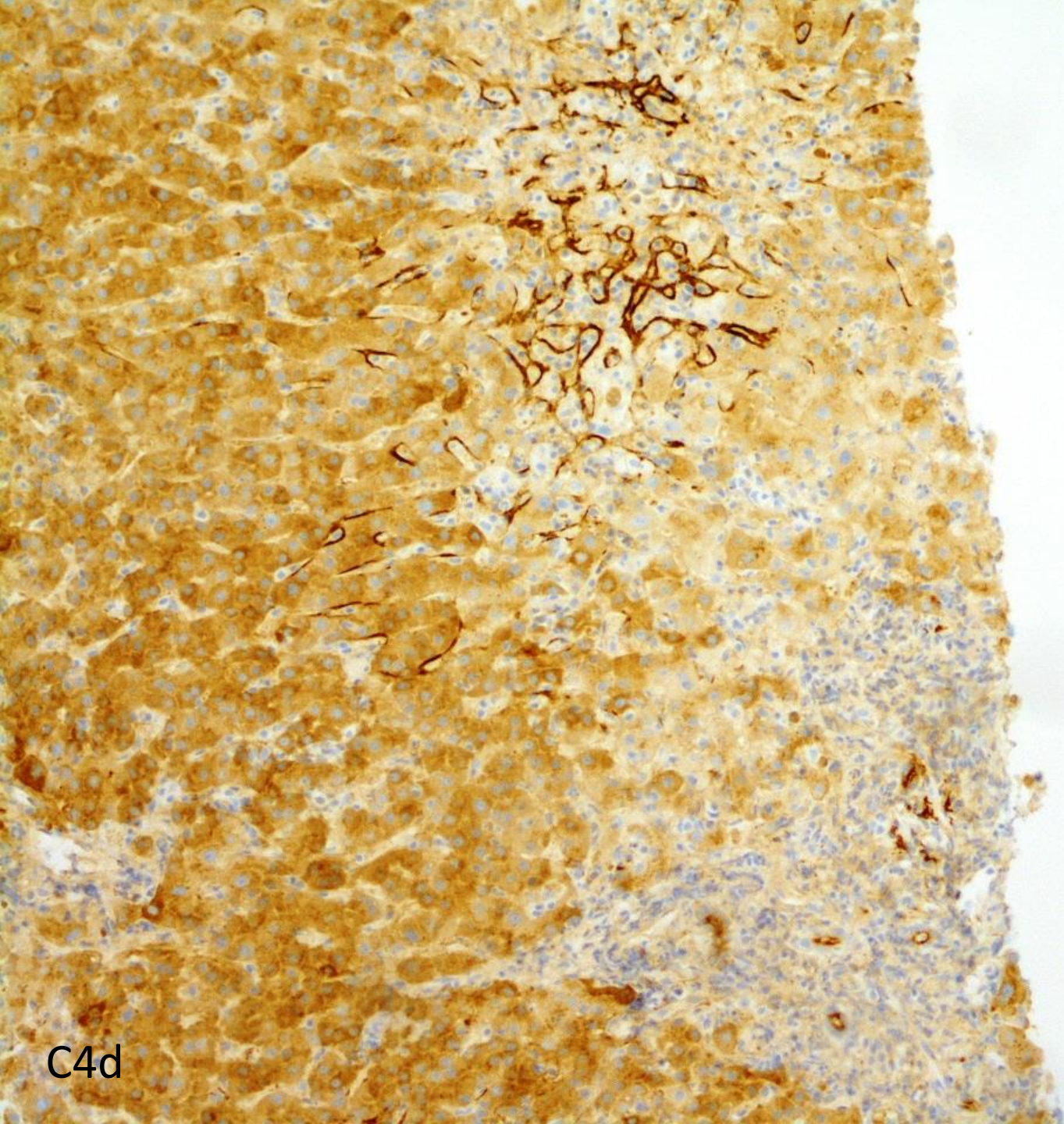


1.00mm

C4d



1.00mm



C4d

1.00mm

- clinical concerns re HEV infection
- Complex immune mediated process, most in keeping with plasma cell rich rejection with associated TCMR and AMR
- Low level of CMV and EBV serology (EBV increased)
- No diagnostic evidence of PTLD (plasmacytic hyperplasia), EBV ISH -
- HEV serology, negative result available shortly after
- Support a diagnosis of on-going rejection
- Plasma cell rich infiltrate, C4d positivity and recent DSA levels all support AMR

- Completed further Methylprednisolone 16th-19th June
- Hydrocortisone 100mg IV OD started instead of Prednisolone 20mg
- Tacrolimus continues but some tablet has been found under her pillow 19/06/2017, further confirmation that medication has partly not been taken
- Death of teenage son (17yo)
- Psychosis
- Issues with nutrition after developing eating disorder
- Currently good levels of immunosuppression
- Remained hospitalised until August
- No further biopsies since

- [Sample 27/06/17: n/a
- ***DSA 7741 MFI (no info if de novo or pre-existent), refers to 30/05/17]

Four liver allograft biopsies showing acute rejection with features suggestive of AMR

- Treatment pre-biopsy
- Clinical information
- Patient compliance
- Repeated biopsies
- ATG / Rituximab
- C4d / Banff 2016
- IgG, IgG4, Plasma cell rich rejection/de novo AIH/
plasma cell hepatitis