

Liver EQA – Circulation LN, Case 12  
Points for Discussion

**Fibrolamellar carcinoma versus conventional HCC**

1. Clinico-pathological features
2. Tumour biology
3. Problems with histological diagnosis

## Fibrolamellar versus Conventional HCC

### Clinico-pathological Features

	<b>Fibrolamellar HCC</b>	<b>Conventional HCC</b>
Age	5-35 years (median 20) (second peak, age 60-70 – Eggert 2013)	Most > 50 years
Sex	M=F	M>F
Aetiology	Unknown	HBV, HCV, alcohol, haemochromatosis
Uninvolved liver	Normal	Usually cirrhotic (Cases occurring in non-cirrhotic liver usually have risk factors for chronic liver disease and pre-cirrhotic fibrosis)
Location	2/3rds in left lobe	No preferential location

# Fibrolamellar versus Conventional HCC

## Tumour Biology

### 1. Molecular pathology

- Differences in gene mutations and molecular signalling pathways
  - e.g. FLC not associated with p53 or beta-catenin mutations , elevated AFP or elevated survivin expression (Liu 2009, Malouf 2012)
- Recent studies have identified a chromosome 19 –linked fusion product involving exon 1 from *DNAJB1* gene and exons 2-10 of *PRKACA* gene (Honeyman , Science 2014; Cornella, Gastroenterology 2015; Graham, Mod Pathol 2015)
  - Present in 79-100% of cases of FLC
  - Not seen in other types of primary hepatic neoplasm (including conventional and sclerosing/scirrhous HCC)
  - Not reported previously in any other type of cancer (Andersen, Gastroenterology 2015)

# Fibrolamellar versus Conventional HCC

## Tumour Biology

- 2. Immunohistochemical phenotype** (Malouf 2009, Vivekanandan 2009, Abdul-Al 2010, Ward 2010, Zenali 2010, Patonai 2011, Ross 2011, Goodman 2012, Patonai 2013, Limaïem 2015)
- FLC more frequently expresses CK 7, EMA, CD68
    - also CD 133 , anterior gradient 2, EGFR
  - FLC less frequently expresses AFP, beta –catenin, CK 19
  - Hep Par 1, pCEA (canalicular) and CD34 (sinusoidal) typically present in both FLC and conventional HCC

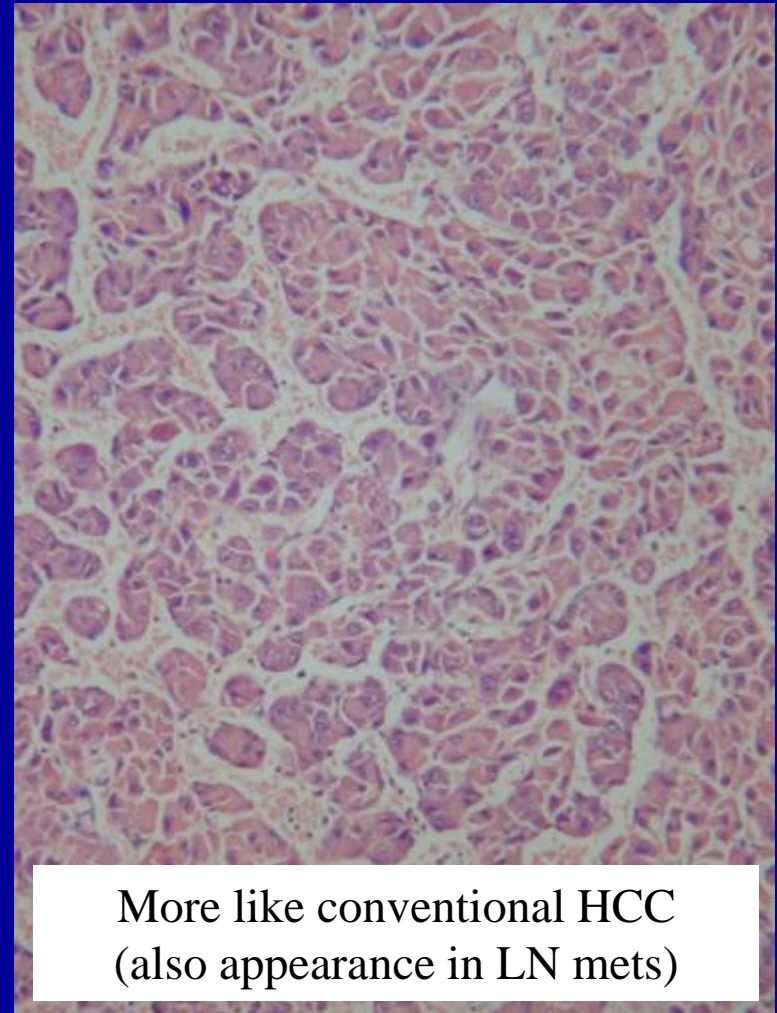
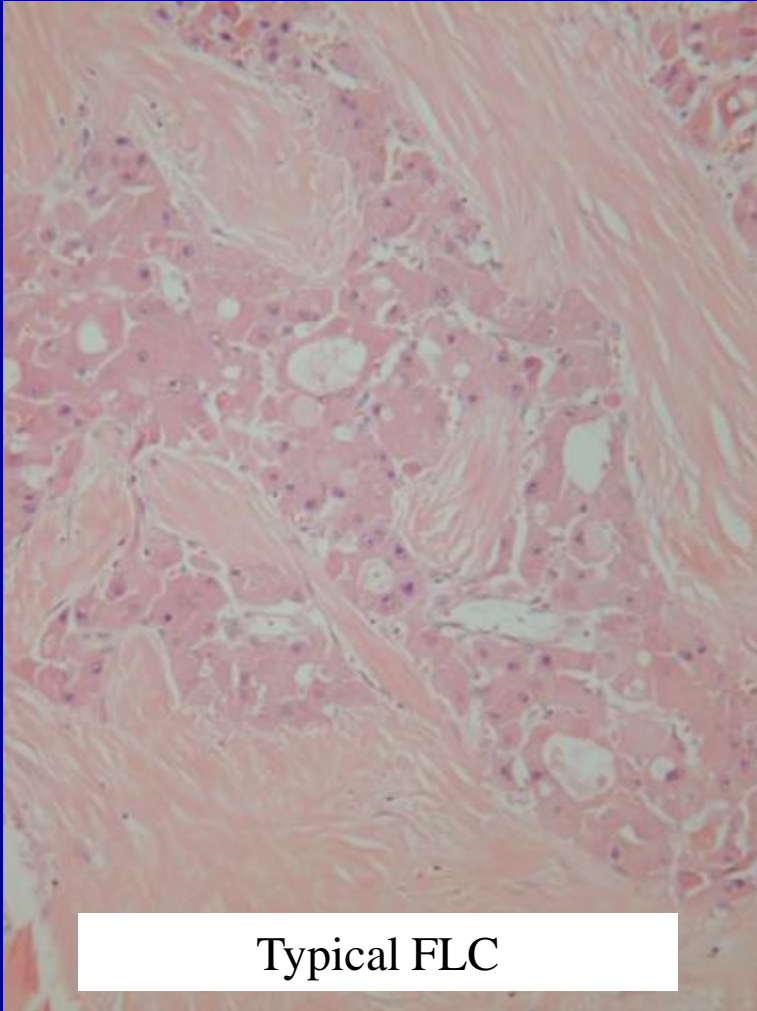
# Fibrolamellar HCC - Problems with Histological Diagnosis

## Cases with Mixed Features of FLC and HCC

### 1. FLC may contain areas resembling conventional HCC

- Mixed features of FLC and HCC present in 10/40 (25%) cases initially diagnosed as FLC (Malouf 2012)
  - Non lesional liver – normal (8), mild fat/fibrosis (2)
  - “Mixed FLC” more frequently occurs in older people, have higher AFP levels and worse prognosis (compared with “pure” FLC)
  - “Mixed FLC” more often associated with intrahepatic recurrence /metastases
- Recent molecular studies of mixed FLC/HCC:
  - 3/3 cases had DNAJB1 -PRKACA fusion transcript described in classical FLC (Griffiths 2016)
  - Another study suggested that mixed FLC have gene expression profile similar to classical HCC (Malouf 2014)

Mixed features of fibrolamellar and conventional HCC  
(Female, age 26 – no underlying chronic liver disease)



# Fibrolamellar HCC - Problems with Histological Diagnosis

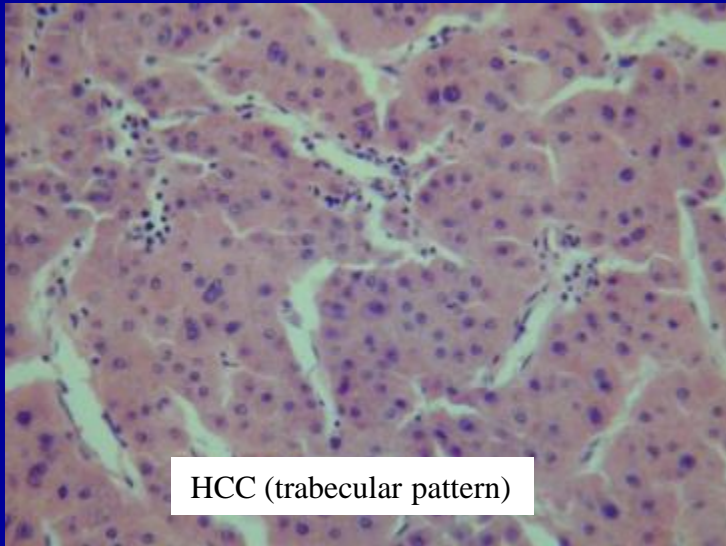
## Cases with Mixed Features of FLC and HCC

### 2. Conventional HCC may contain areas with a resemblance to FLC (sclerosing or scirrhous HCC)

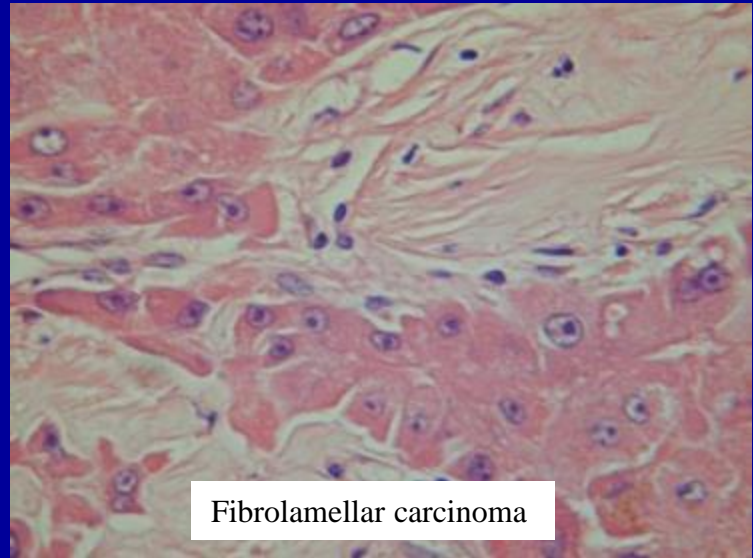
- a. Cases of HCC occurring in non-cirrhotic liver may be variant of intrahepatic cholangiocarcinoma (or mixed HCC/CC)
  - Stroma loose and cells smaller than in FLC
  
- b. Typical HCCs in cirrhotic liver may contain foci with cytological features and/or stroma resembling FLC
  - Infrequent case reports
  - Functional significance uncertain

# HCC with Foci of FLC

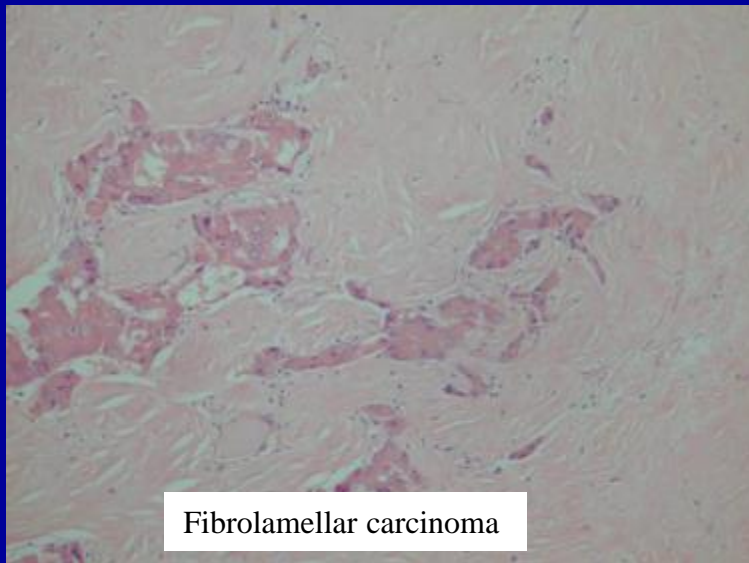
Female, age 67. Liver transplant for NASH. 3.5cm nodule in right lobe



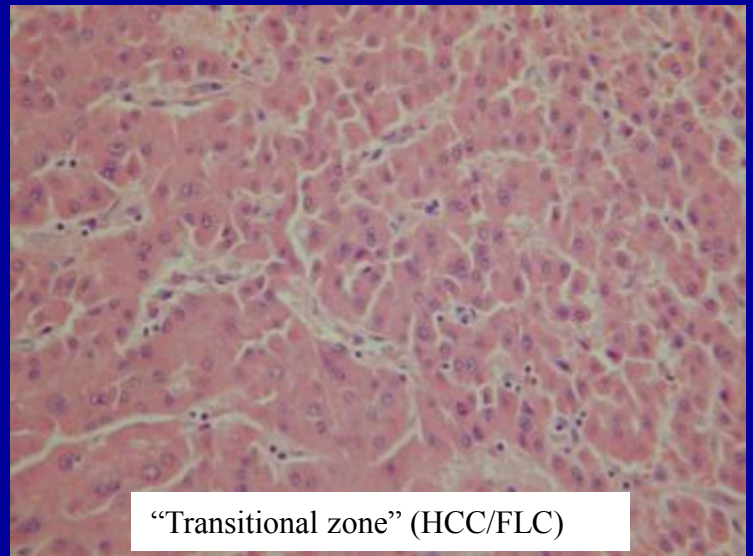
HCC (trabecular pattern)



Fibrolamellar carcinoma

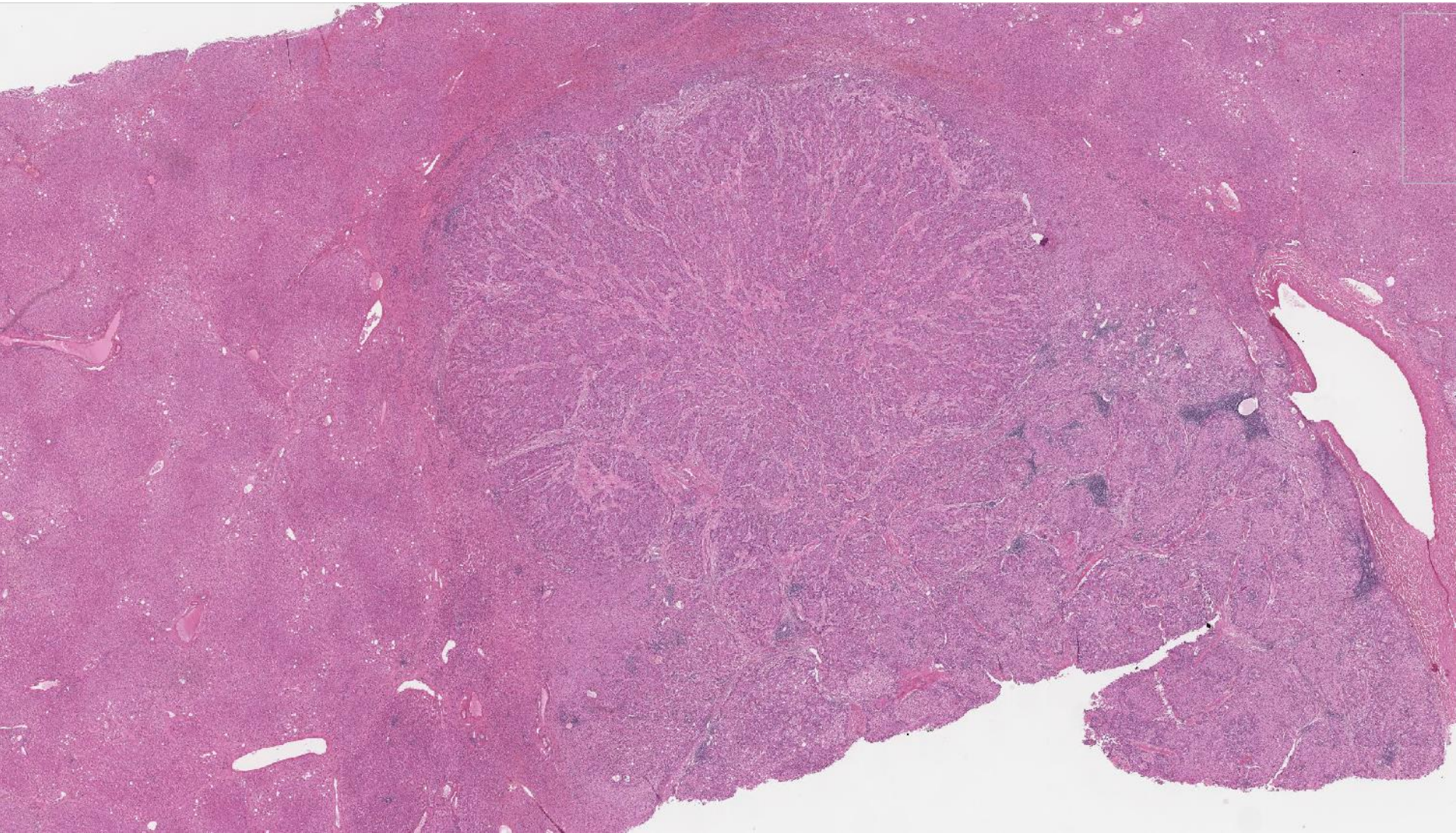


Fibrolamellar carcinoma

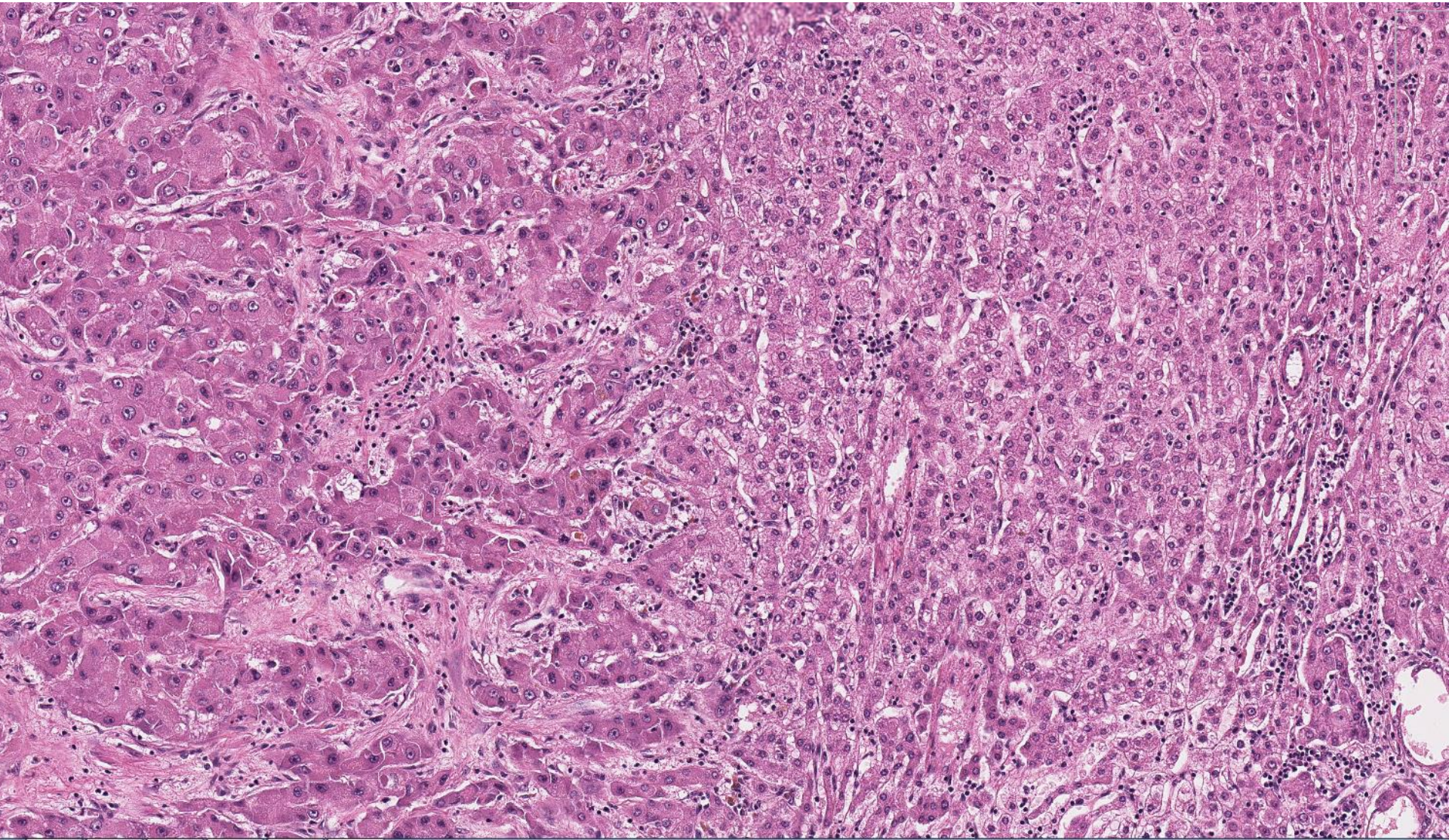


"Transitional zone" (HCC/FLC)

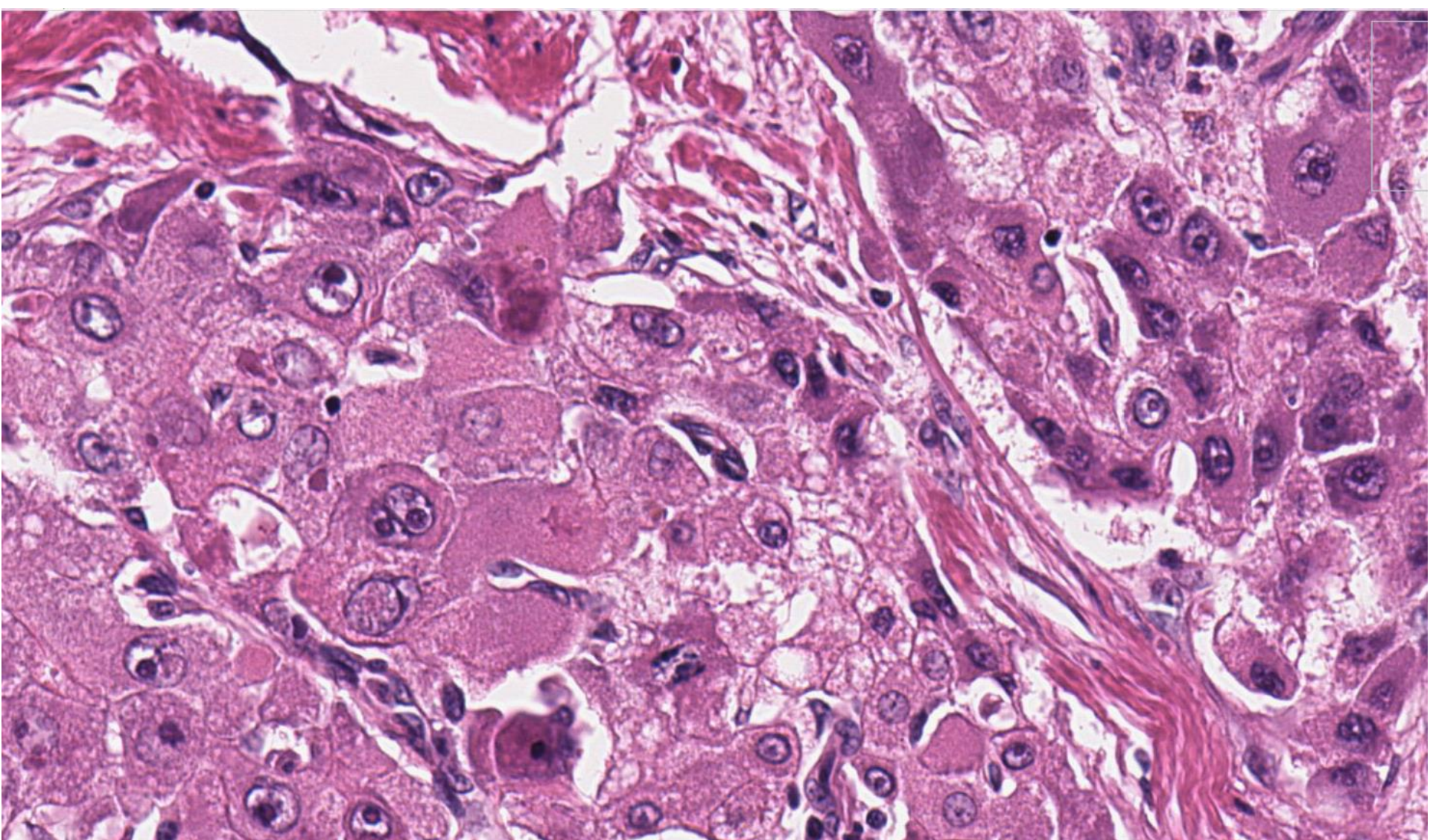
## Circulation LN – Case 12



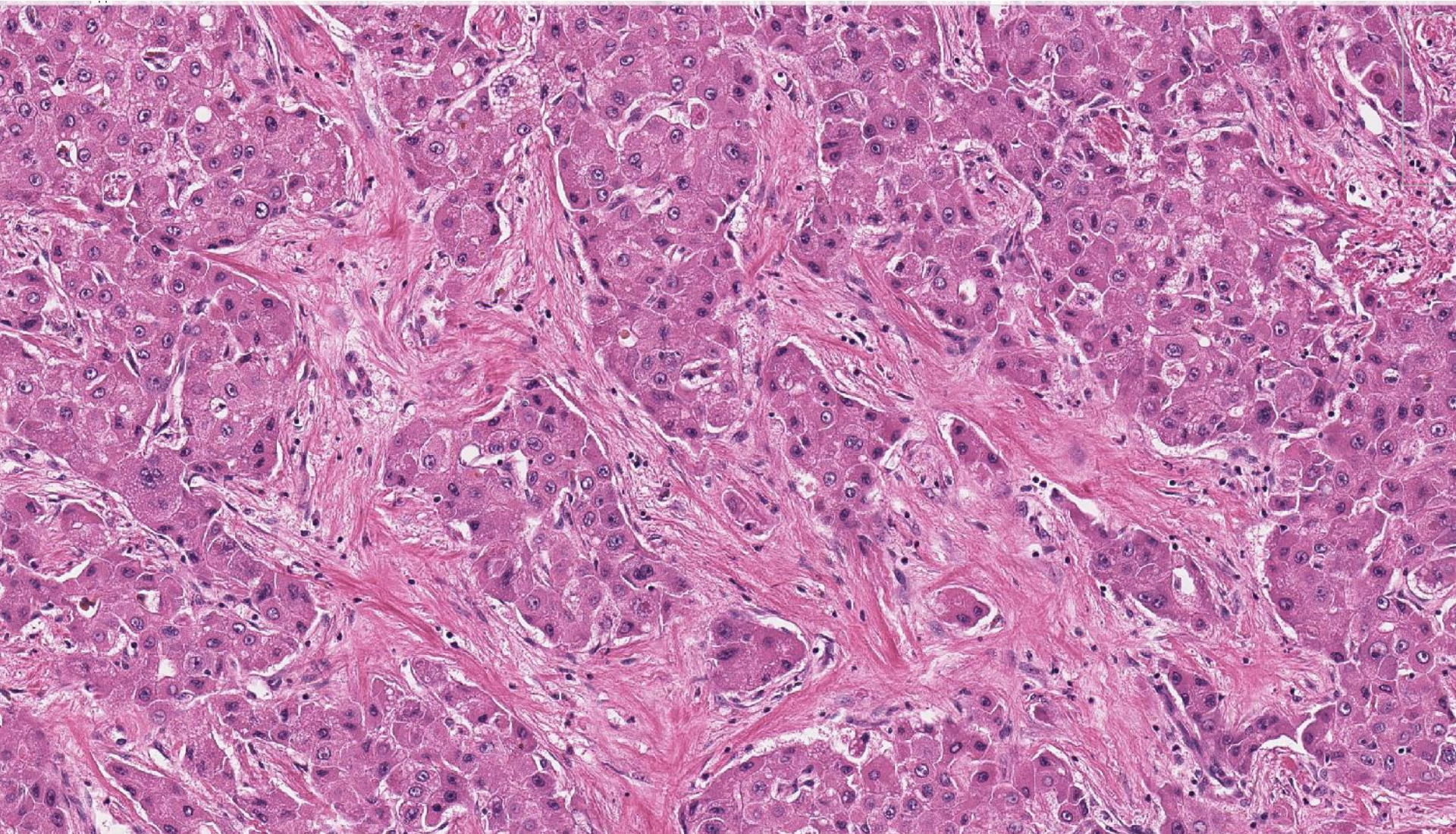
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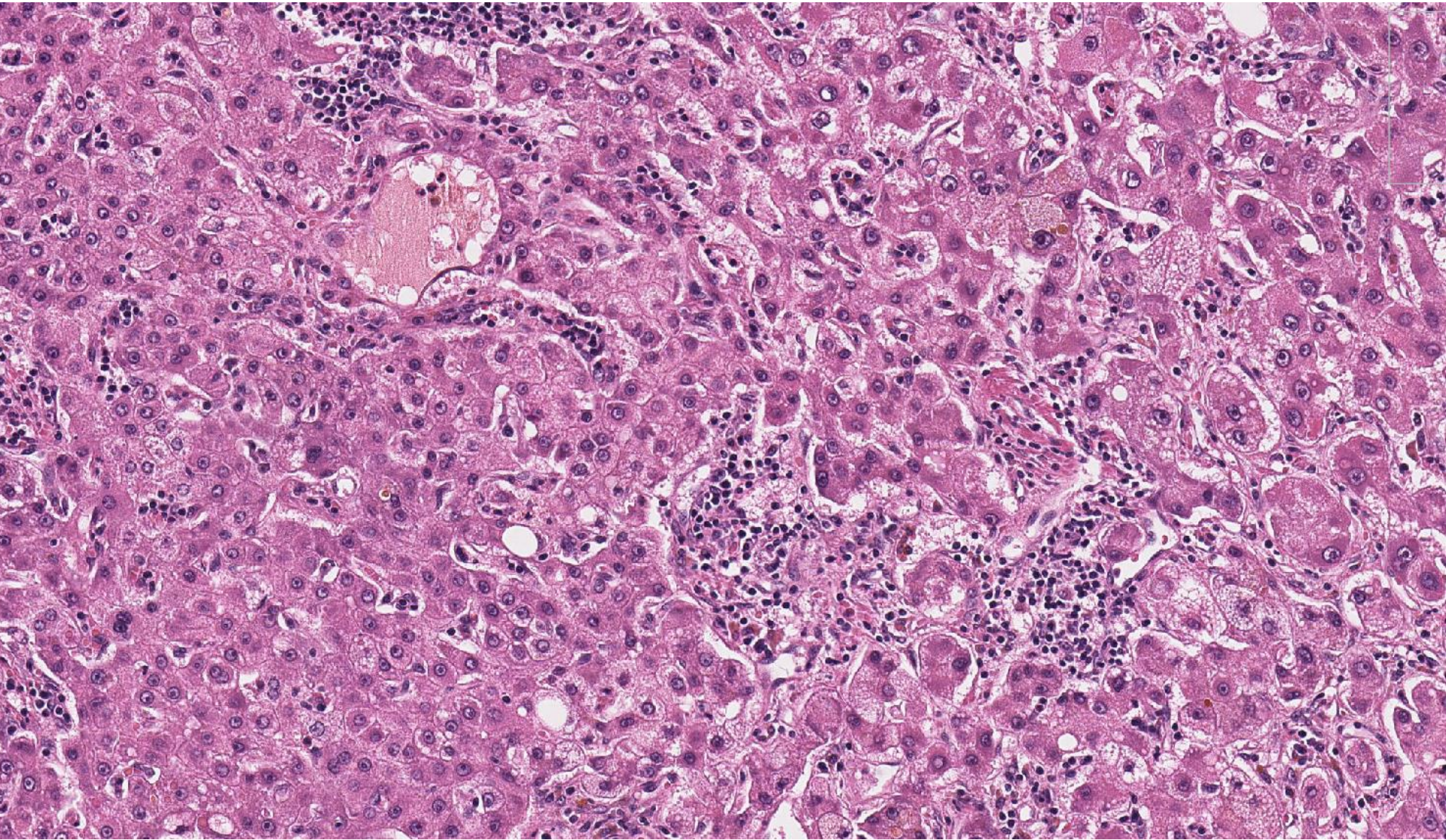
## Circulation LN – Case 12



## Circulation LN – Case 12



## Circulation LN – Case 12



**Circulation LN – Case 12**  
**Non-lesional Liver**

