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LETTER

Beyond scoring: a modern histological assessment of chronic hepatitis should include tissue angiogenesis

We read with great interest the leading article by Rosselli *et al*[1] which offers a contemporary perspective to the clinical issue of interpreting progression (and regression) of chronic liver diseases (CLDs).

We fully agree with the view that the histological scoring of fibrosis is a reductive approach to the assessment of CLDs, as it does not fully reflect the complex events involved in the progression to cirrhosis. As suggested by Rosselli *et al*, a more insightful morphological analysis of liver biopsy should consider other important factors contributing to disease progression/regression, and possibly to cancer development. Angiogenesis represents one of such key factors.

Liver angiogenesis is a pathophysiological process characterised by changes in the phenotype of sinusoidal endothelial cells, which assume the features of capillary endothelial cells. This process, known as sinusoidal capillarisation (SC), can be routinely assessed by CD34 immunostaining, that results negative in normal liver sinusoids and positive in the capillarised ones (figure 1).[2]

Liver angiogenesis and fibrogenesis are closely related pathogenic mechanisms, concurring to the progression of CLDs and to the development of portal hypertension. Furthermore, neoangiogenesis represents a determinant factor affecting the reversibility of hepatic fibrosis and the development, progression and metastatic potential of liver neoplasms.[3]

Despite these clinically relevant evidences, angiogenesis still remains largely neglected in routine diagnostic practice. Based on such observations, we investigated the clinical implications of neoangiogenesis in a cohort of patients with CLD.

A series of 40 liver biopsies obtained from subjects with post-transplant recurrent chronic HCV hepatitis was considered. Fibrosis was staged according to Ishak's system and SC was immunohistochemically evaluated with a monoclonal anti-CD34 antibody (QBEND-10; dilution 1:10), SC was defined as absent (CD34-negative sinusoids), periportal (CD34-positive sinusoids around portal tracts) and diffuse (CD34-positive sinusoids extending into the lobular parenchyma) (figure 1). Portal microvessel density was also estimated and graded in a three-tiered score, as previously reported.[2]

The histological results were correlated with splanchnic haemodynamic parameters, obtained at the time of liver biopsy (portal blood flow velocity (PBV), hepatic artery pulsatility index, splenic artery pulsatility index and portal hypertension index).[4] Cases with a diagnosis of rejection or vascular alterations (ie, portal/arterial thrombosis or stenosis) were excluded, since these conditions may alter splanchnic Doppler parameters.

The majority of cases were characterised by low stage fibrosis (score 1–2=31 cases; score 3–4: 7 cases; score 5–6: 2 cases); HAI ranged from 3 to 10 (mean value 5.90 ±2.24). SC was observed in 57.5% (23/40) of biopsies (periportal capillarisation: 13 cases; diffuse capillarisation 10 cases). A significant correlation was found between splenic artery pulsatility index and SC (Spearman's r p=0.02). SC also significantly correlated with reduced PBV (two-sided t test: p=0.0001) and with higher portal hypertension index (p=0.0007). Higher grades of microvessel density were significantly associated with fibrosis score >2 and with higher HAI, while only a trend of association was observed with reduced PBV.

To the best of our knowledge, this is the first evidence of a correlation between histologically assessed liver angiogenesis and Doppler-documented haemodynamic changes. Notably, despite SC, most of our cases featured low fibrosis stage: this confirms that angiogenesis represents an early event during CLDs, whose evaluation may provide adjunctive and valuable information.

In conclusion, our observation strongly supports that tissue angiogenesis should become part of the histological assessment of CLDs and prompts further studies addressing its role at different stages of liver fibrosis.

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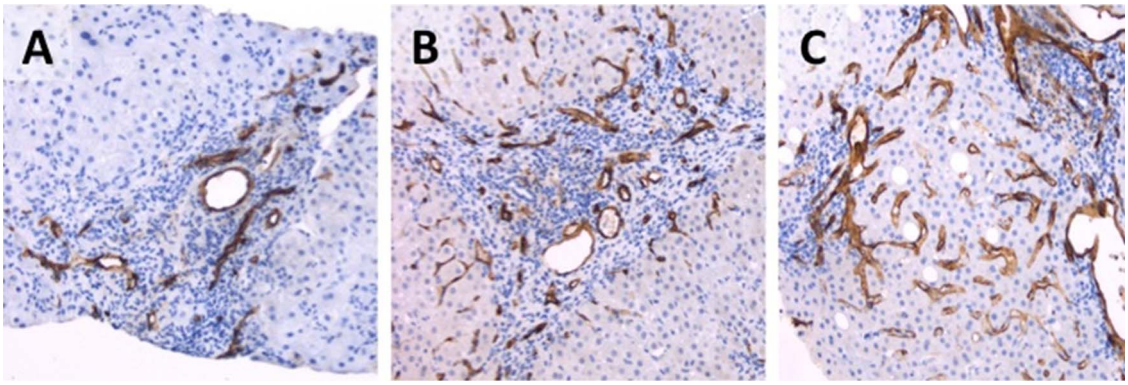

Figure 1 Immunohistochemical assessment of sinusoidal capillarisation. Normal sinusoids stain negative for CD34, while portal vascular structures result consistently positive (A). Periportal (B) and diffuse (C) capillarisation, with sharp positivity for CD34. (CD34 immunostaining; original magnification ×20).

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