Dynamic Fibrosis Features in Post-treatment Biopsies and its Interpretation

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Background/Aim

Fibrosis staging has been consistently reported to be a key histological determinant of clinical outcomes for patients with non-alcoholic steatohepatitis (NASH), making it crucial to accurately evaluate fibrosis.

Given liver fibrosis dynamics, it is not rare to observe an overlap of fibrosis features from different stages within the same biopsy sample during disease regression. While fibrosis regression as a concept is commonly understood and accepted, it remains unclear if current staging systems are sufficiently robust to document the regressive fibrosis changes, especially those observed in post-treatment biopsies in NASH clinical studies.

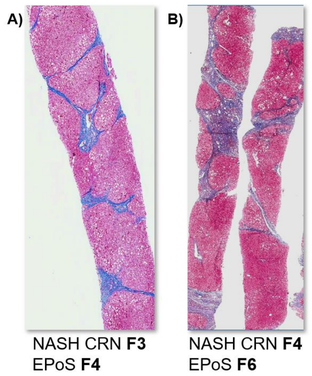
Methods

The images used in this study are from lifestyle and surgical intervention NASH patients. The biopsies interpretation performed within this poster represents the opinion of the authors.

Liver biopsy images are obtained with courtesy of Dr. Pierre Bedossa.

Second harmonic generation/two-photon excitation fluorescence (SHG/TPEF) image is obtained from Genesis™ system and analyzed by qFibrosis® (HistoIndex, Singapore).

Results and Discussion



In the natural progression of a disease as seen in non-treated NASH samples, (Figure 1), we observe clear fibrosis features with no overlap i.e. the sample shows many septa without nodule throughout the biopsy (Figure 1, A); or cirrhosis with complete nodulation (Figure 1, B).

With intervention in most chronic liver disease clinical trials however, we begin to observe a mixture of fibrosis features in patients' biopsies and fine features of fibrosis regression may be missed since the semi-quantitative system defines a stage by narrow set of requirements.

Figure 1. Both liver biopsies are of a typical non-treated NASH samples showing defined fibrosis features according to either the NASH CRN or EPoS system.

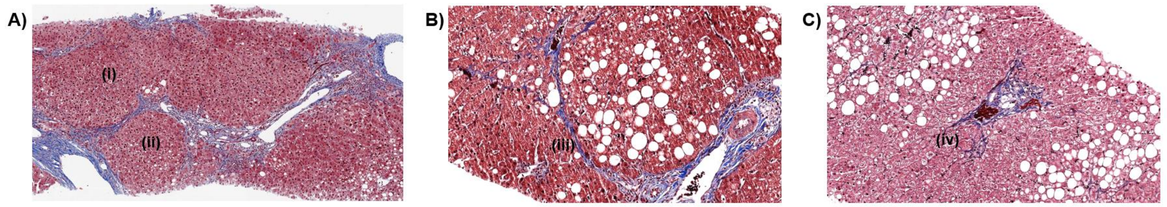


Figure 2. Various liver biopsies obtained from patients with NASH which seems to be showing fibrosis regression at different stages. **A) Regressing cirrhosis:** Nodulation is vaguely observed [refer to (i) and ii], with thinning septa; **B) Septa regression:** Fibrous septa [refer to (iii)] are extremely thin; **C) Portal fibrosis:** Extremely thin fibrosis spikes around the portal tract.

The images shown in Figure 2 are examples of what can be interpreted as fibrosis regression in NASH patients. Figure 2A represents a regressing cirrhosis, with nodulation still observed at (i) and (ii), though fibrous septa appears compressed potentially leading to incomplete septa cirrhosis. In Figure 2B, the fibrous septa as observed in (iii) is extremely thin and densely compacted, which is indicative of septa regression. Lastly in Figure 2C, we observe some thin fibrosis spikes in (iv), likely arising from regeneration of hepatocytes which infiltrated into thin septa. It is noteworthy that this portal fibrosis feature is different from that of a periportal fibrosis progression, in which small collagen fibers dissect the periportal area.

By conventional definitions, a higher stage is likely to be called if e.g., thinning septa is observed with a cirrhotic nodule. But with drug intervention in clinical studies, the current staging system may be insufficient to address the possibility that a cirrhotic sample could be showing regressing cirrhosis.

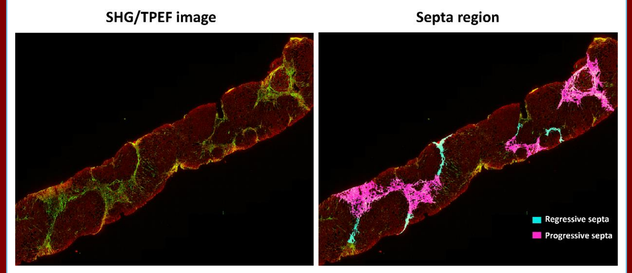


Figure 3. SHG/TPEF image of a liver biopsy obtained from patient with NASH.

Using qFibrosis, regressive and progressive septa within liver biopsies can be automatically detected and differentiated when both features are observed on the same biopsy sample.

Conclusions

- Fibrosis regression may not proceed in a similar linear manner as fibrosis progression
- Current standards of evaluation uses the same staging system for the evaluation of both fibrosis progression and regression
- We propose that an integrated semi-quantitative scoring and quantitative approach would provide a more comprehensive evaluation of fibrosis regression in post-treatment biopsies for NASH clinical studies

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