Original article

Biopsy in chronic liver disease: proposal for a shared path between clinicians and pathologists

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Summary

Introduction. Liver biopsy is fundamental for characterizing chronic liver disease. Effective communication between specialists during the diagnostic process is crucial. This project aims to outline a diagnostic path shared by clinicians and pathologists, and to propose practical solutions at different stages of the diagnostic work-up, from clinical suspicion to the histology report in patients with chronic liver diseases.

Methods. A panel of experts, within the methodological framework of lean management, joined two rounds of discussion sharing their professional experiences. They reached an agreement on the essential phases and actions of the diagnostic process, and built a shared diagnostic workflow.

Results. The panel agreed on the importance of a standardized form to be filled with all relevant clinical and laboratory data to ensure the flow of information between the clinician and the pathologist. Further decisions were reached on the following practical issues: the advantage of performing liver biopsies in dedicated centers, the need for homogeneous procedures, and the minimum quality standards in all phases, including reporting. Finally, the panel agreed on the usefulness of digital pathology to exchange observations and opinions and to create a territorial network to discuss challenging cases.

Conclusion. Sharing a diagnostic path between the pathologist and the clinician can be a powerful tool to improve both the timing and accuracy of the histology report.

Key words: Chronic liver diseases, liver biopsy, diagnostic pathway, lean management

Introduction

Historically, liver biopsies have played a central role in chronic liver disease, representing a key tool for both diagnosis and prognostic definition [1]. In recent years, the refinement of less invasive, highly specific, and sensitive diagnostic techniques has led to a decreasing request for biopsies [2] and a consequent global reduction of liver biopsy procedures. Non-invasive techniques include: blood tests, methods assessing physical properties of the liver tissue (e.g. liver stiffness), and imaging methods. However, non-invasive diagnostic tools are burdened by some limitations. For instance, the results of blood tests can be affected by extra hepatic chronic diseases and liver stiffness measurement can overestimate fibrosis in case of inflammation, steatosis and other conditions [3].

Despite these advancements, liver biopsy remains a crucial method for evaluating several chronic liver diseases where histological analysis is still fundamental. It is particularly important in specific situations, such as when multiple underlying factors are suspected—like autoimmune hepatitis combined with primary biliary cholangitis (PBC) or autoimmune hepatitis paired with metabolic associated steatohepatitis [2,4,5] or when there is inconclusive serological data and diagnostic uncertainties [2]. Moreover, liver biopsy allows assessing disease severity, including staging and grading [2]. This information is necessary to refine prognosis and is also predictive of response to therapy. For example, in patients with PBC the response to ursodeoxycholic acid (UDCA) is lower in patients with advanced fibrosis at diagnosis, which exposes them to a risk of more rapid disease progression [1]. Despite the importance of biopsy in defining liver disease, there are some challenges. These include the heterogeneity of histological features, and the presence of non-specific patterns, especially in the early phases of the disease, which can affect the final diagnosis. For these reasons, the presence of a trained and experienced pathologist to interpret liver histology, and the access to a sharing network for comparison and/or review are necessary and recommended [1,6].

Furthermore, collaboration between the expert liver pathologist and the clinician is essential. Effective communication between these professionals plays a vital role in the diagnostic and therapeutic process [6]. Diagnostic investigations require close collaboration with the clinician to assure optimal reliability and information [7].

A close interaction between the specialists involved is essential to make the clinical suspicion meet the morphological features, to guarantee the diagnostic accuracy and the most appropriate therapy. Currently, there are no operational models shared at a national level. Therefore, establishing a standardized clinical-pathologic approach can be a practical solution to overcome the difficulties in liver biopsy interpretation and consolidate the dialogue between the pathologist and the clinician, which is vital to guide the diagnostic process.

The aim of this expert opinion was to identify a structured and standardized diagnostic process, resulting in an improvement of the diagnostic performance in terms of both accuracy and Turn-around Time (TAT).

Methods

A panel of 23 experts from Central and Southern Italy was selected to participate in the discussions. Most were listed among the authors of the present publication. The selection criteria included: i) documented clinical experience; ii) traceable publications in scientific journals; iii) different backgrounds and professional experience (e.g. hospital size, geographic location). The panel included both pathologists and hepatologists. There were two full-day discussion rounds aimed at identifying an integrated diagnostic approach for chronic liver diseases. The sessions focused on identifying an integrated diagnostic approach for chronic liver diseases, defining the standards for interaction between clinicians and pathologists, and developing a network of communication, also with digital health tools. A moderator led the discussions in both rounds following the lean management approach. In the healthcare sector, this approach aims to create maximum value for the patient by reducing waste and long waits [8]. This is a methodological approach borrowed from the entrepreneurial field, which is based on the analysis of processes and the identification of resolution strategies. According to this method, the project was divided into two phases: mapping and optimization. The mapping phase described the current situation, according to the panelists' experience, highlighting the critical issues regarding clinical suspicion, the indication for a liver biopsy, its execution, the interpretation of the histology with the production of a report, the establishment of a definite diagnosis, and the consequent access to therapy.

The actions to undertake and the operational suggestions for defining a standard path were analyzed in the optimization phase. In both phases, a step-by-step procedure was adopted.

The scope was to simplify the process flows, optimize resources, and increase production value within a complex organization.

The first step of the process was the identification of the "value" to be achieved that, in this case, consisted

of reaching the correct diagnosis within an adequate time, allowing to establish the appropriate therapy as soon as possible. This was followed by the mapping phase, in which the entire process was evaluated to identify critical issues and unmet needs. Finally, through the optimization phase, improvement and resolution actions were placed and shared, so the procedural standards were defined. The optimization phase concluded with the definition of a standard process.

RESULTS

MAPPING PHASE

The diagnostic path starts from the clinical suspicion and the indication for a liver biopsy, and develops through its execution, the interpretation of the histology with the production of a report, the establishment of a definite diagnosis, and the consequent access to therapy. Each of these steps was analyzed to highlight its characteristics and critical issues.

STEPS 1 AND 2: ACCESS TO THE BIOPSY, PROFESSIONAL FIGURES INVOLVED, AND INFORMATION FLOW

The biopsy is performed based on a clear indication, to avoid inappropriate tests. The suitability of the indication should be established according to well-defined criteria, depending on the clinical suspicion. The biopsy is an invasive test and, although considered safe, it carries the risks inherent to all invasive procedures. Therefore, it should be considered as an ancillary tool for the clinician, to be chosen when non-invasive diagnostic tools are inconclusive; its execution should be necessary and balanced by the benefits it can bring to the management of the patient.

The professionals involved are the clinician, who indicates the need for a biopsy, the specialist who performs the biopsy (usually a dedicated clinician or a radiologist), and the pathologist, who is in charge of the preparation and interpretation of the histological sample. The pathologist should be a highly specialized figure dedicated to liver disease. Expertise is crucial for a valid and accurate interpretation of liver biopsies. In centers where this figure is missing, it is advised to ask for an expert consultation. The establishment of a network of reference centers would favor consultation and second opinion on difficult cases.

Each figure involved in the diagnostic work-up should be aware of the indication for the biopsy. For this reason, exchange of information through pre-printed, shared formats and regular meetings is advisable.

STEPS 3, 4 AND 5: THE BIOPSY, STANDARDS AND MINIMUM REQUIREMENTS

Biopsy should be performed in referral centers for non-neoplastic liver disease. It is essential to define standard, both for sampling procedure (minimum sampling requirements) and for tissue fixation. This standard aims first and foremost to produce a sample suitable for analysis, but it is also functional in setting a path without waste resulting from procedural errors and/or redundant steps, optimizing the timeframe.

When interpreting the liver biopsy, the pathologist should already possess all information detailing the specific clinical context and why the examination is taking place. Therefore, a clinical description of the case should always accompany the biopsy sample. If necessary, further consultations between the pathologist and clinician should be easily achieved. An ad hoc meeting discussion for sharing complex cases is advisable, not only during the diagnostic phase but also, based on the evolution, for the re-evaluation of cases over time.

Concerning the histology report it is important to define a standard, identifying the essential elements to be represented in a liver biopsy report (minimum reporting requirements). The description must be sharp, use intelligible language and contain all the details to produce an informative, homogeneous, and shareable report. Finally, the report should be accessible and usable for the applicant.

STEPS 6 AND 7: DIAGNOSIS AND THERAPY

The diagnosis is the outcome of the process that enables access to appropriate therapies. Therapy is usually subordinate to accomplishing a quick diagnosis, so a delay of the histology report could affect timing of therapy. In some cases, a strong clinical suspicion may be considered adequate in order to undertake treatment, only requiring further re-evaluation in light of the histological examination report. In others, the lack of response to therapy may constitute an indication for a liver biopsy and be the basis for a diagnostic review.

Given the complexity of the diagnosis and management of chronic liver diseases, a network joining expert clinicians and pathologists together could facilitate ongoing and valuable discussions about the diagnostic and therapeutic process, fostering mutual scientific growth.

OPTIMIZATION PHASE

After mapping the process and identifying the needs of each phase, the actions to undertake and the operational suggestions for defining a standard path were discussed (Tab. I).

STEPS 1 AND 2. CLINICAL SUSPICION AND INFORMATION FLOW

At this stage, the drafting of a standardized form for chronic liver disease (Tab. II), containing clinical infor-

Table I. Operational indications for the definition of a standard route.

Steps 1-2 **Clinical suspicion and information flow**	**I.** The appropriateness of the indication for liver biopsy derives from clinical suspicion, according to guidelines and expertise of the clinician. **II.** A standardized clinical card produces procedural clarity and correct transmission of the information flow.
Steps 3-4 **The biopsy: standard of execution**	**I.** For diffuse liver disease, the biopsy should be performed using a needle with a diameter of 16-17 gauge. **II.** The amount of material taken should be no less than 20 mm and not fragmented. The higher the quantity, the better the withdrawal. **III.** The biopsy sample should be accompanied by a description, carried out by the proceduralist, which contains information on the number of fragments taken and possibly on the site (optional).
Steps 3-4 **The biopsy: Standard preparation of the sample**	**I.** To guarantee diagnostic adequacy, the preparation of the sample should meet the minimum standard requirements, providing for some stains considered essential (Table 2) **II.** Any further staining will be at the discretion of the pathologist.
Steps 5 **Reporting standards**	**I.** The liver biopsy report should guarantee inter-operator uniformity, be clear and complete in form. **II.** A descriptive checklist containing the minimum diagnostic requirements constitutes a standard of quality and homogeneity and a support for the pathologist in the reporting process. **III.** The histological diagnosis formulated can be more or less conclusive. A disease staging should accompany the presumed diagnosis, according to a suitable scoring system or accurate descriptors.
Steps 5 **Timing (*turnaround time* - TAT definition).**	**I.** A TAT of 10 working days is recommended in 75% of cases (good practice recommendation).
Steps 6-7 **Diagnosis and therapy**	**I.** Only a consolidated collaboration between clinician and pathologist allows the adequacy and quality of the diagnosis to be achieved. **II.** The construction of an exchange platform between pathologists who are experts in liver diseases and hepatologists could represent a tool for individual and collective growth. **III.** The adequacy and timeliness of access to therapy follows from the correctness of all the previous phases of the diagnostic process. **IV.** Strong clinical suspicion can give direct and empirical access to therapy, while awaiting the liver biopsy report with a possible diagnostic review.

mation (anamnestic data and tests carried out), guarantees that the elements that led to the clinical suspicion are clearly described and constitute the ideal tool to ensure the flow of information between the various players in the process (from the clinician to the pathologist).

STEPS 3 AND 4. THE BIOPSY: EXECUTION STANDARDS AND PREPARATION STANDARDS OF THE SAMPLE (FIG. 1 AND FIG. 2)

The biopsy is carried out by the proceduralist. From practical point of view, a 16-17-gauge needle and a non-fragmented sample with a minimum length of 20

Table II. Standardized medical record for liver disease with indication for liver biopsy.

Description	Variables
Age	Years
Gender	F/M
Acute clinical onset	Y/N
Clinical/laboratory onset	< 6 months / > 6 months
Medical history	Drugs - alcohol - associated pathologies - family history of liver diseases
Biochemistry / Serology	ALT - AST - GGT - ALP - total and direct bilirubin - gamma globulins - autoimmunity - viral markers - complete blood count - platelets - albumin
Normal ultrasound	Y/N
MRI /CT scan	Not performed / performed; within the norm - outside the norm
Clinical suspicion	Metabolic/toxic/cholestatic/autoimmune liver disease - etc.

AST, aspartate transaminase; ALT, alanine transaminase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; MRI, magnetic resonance imaging; CT, computed tomography.

mm guarantee an adequate sample.

The preparation of the slides involve fixation, cutting, and staining of the sample. A minimum standard number of slides and staining is defined to obtain homogeneity in the histological evaluation and avoid procedural waste of time. A set of the most useful stains is provided in Figure 3. Any further request for staining will depend on the pathologist's judgment based on the clinical suspicion.

POINT 5. REPORTING STANDARDS AND TIMING (FIG. 1)

The report of a liver biopsy is structured into a descriptive component (macroscopic and microscopic) and a diagnostic conclusion (histological diagnosis). A report should meet quality standards to be adequate, which means it must be clear and complete and should con-
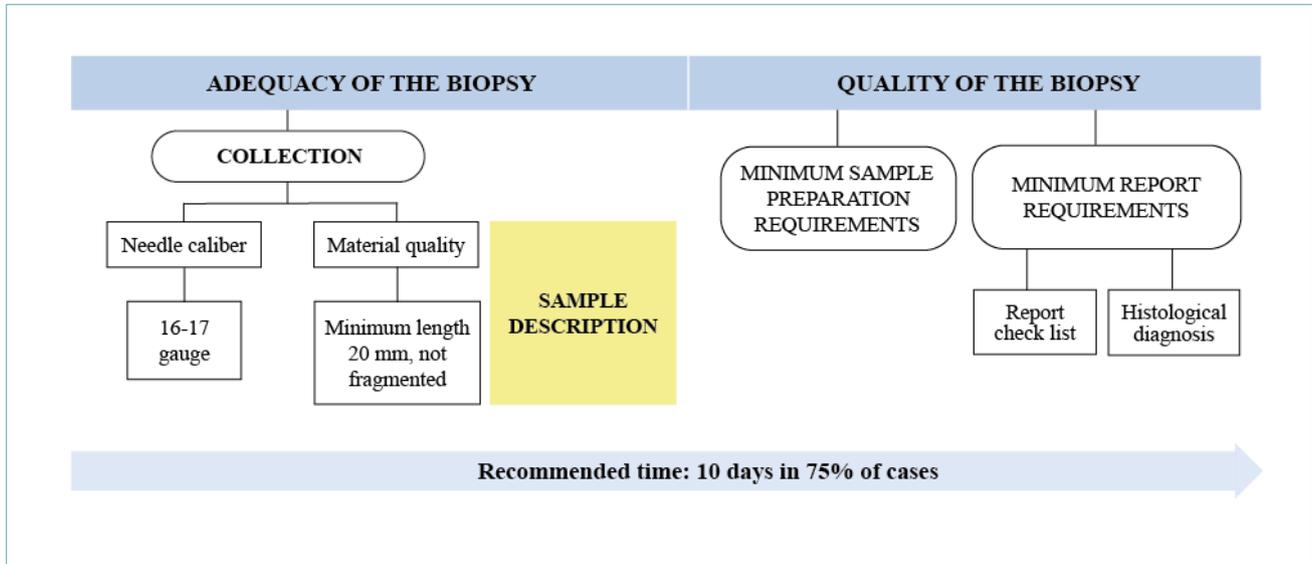

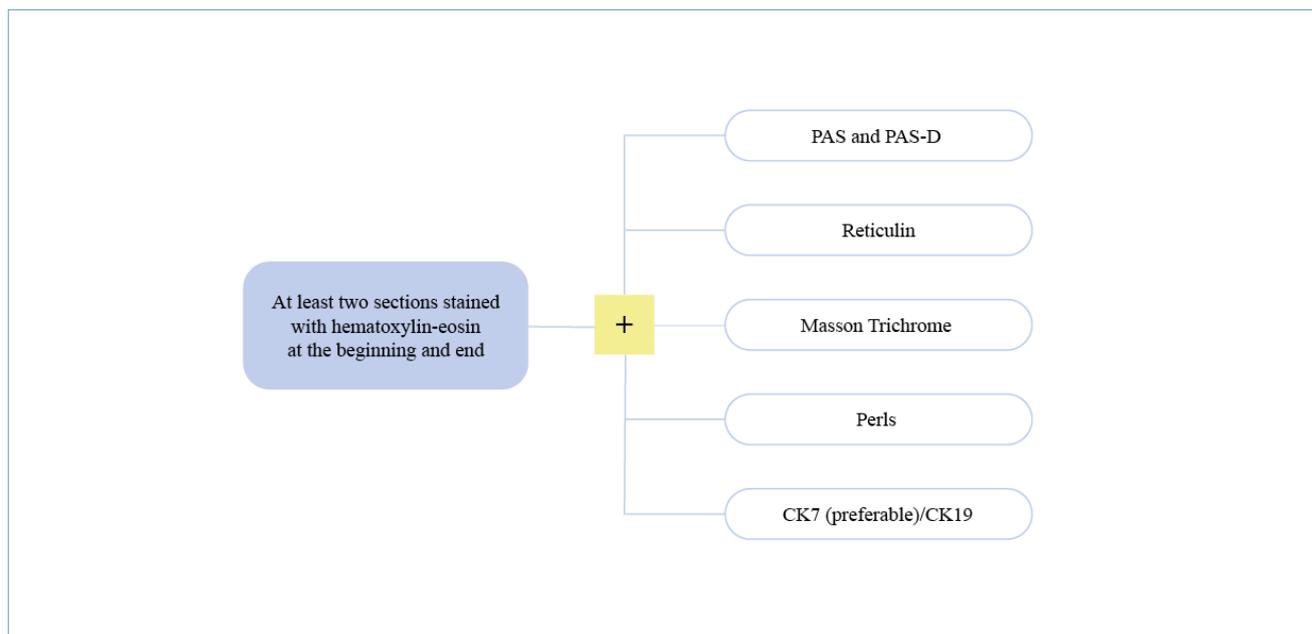**Figure 1.** Definition of adequacy and quality criteria for the biopsy.

Figure 2. Minimum sample preparation standard.
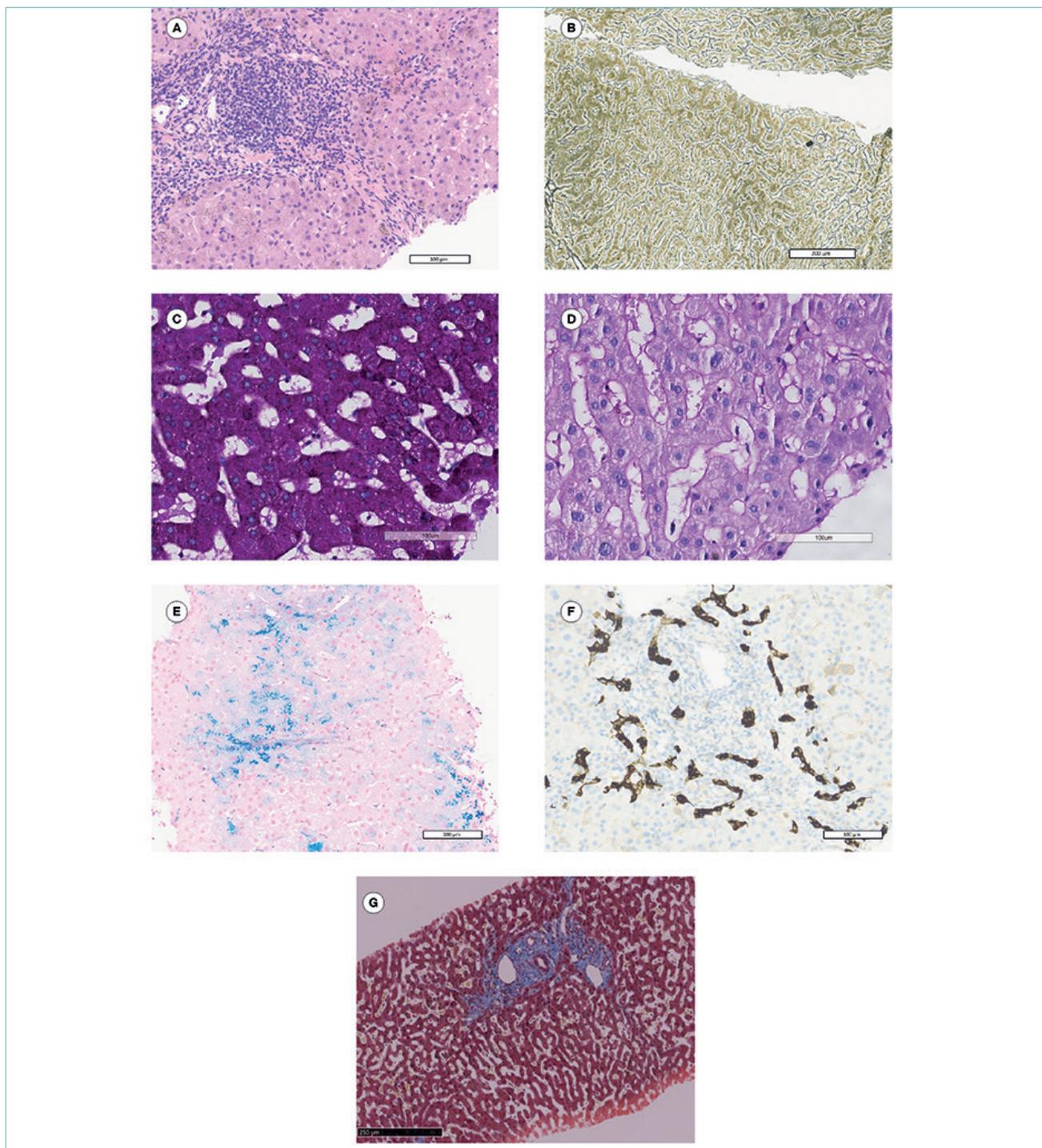PAS, Periodic Acid-Schiff; PAS-D, PAS Diastase stain.

Figure 3. Required stains. (A) H&E staining demonstrates moderate portal nodular inflammation that spares the biliary duct, along with interface hepatitis and hemosiderin overload in the cytoplasm of hepatocytes in a patient with beta-thalassemia (original magnification: 20x). (B) The reticulum stain highlights a preserved lobular architecture and reticulin network, showing slight regenerative features of the hepatocytes in what appears to be an almost normal liver biopsy (original magnification: 10x). (C) PAS stain highlights the glycogen content of normal hepatocytes (original magnification:20x). (D) PAS/D stain. After treatment with diastase glycogen is not detected in the hepatocytes (original magnification: 20x). (E) Perls stain displays coarse hemosiderin granules in both periportal hepatocytes and portal macrophages in a Beta-Thalassemia patient (original magnification:20x). (F) CK7 staining reveals damage to the central duct, ductular reaction, and loss of Heiring channels in an overlap variant AIH-PBC (original magnification:20x). (G) Trichrome stain highlights the size of the portal tract with the portal vein, artery and bile duct (original magnification: 10x).

tain the minimum requirements necessary for diagnosis. A standardized report format has been outlined to meet these needs, including a checklist of the sample description and the diagnostic conclusion (Tab. III).

The use of a checklist supports the pathologist during the reporting process, ensuring uniformity of the reports. All the features defined in the minimum standards should be represented in the report.

The histological diagnosis in the report can be confident or probable. When the biopsy allows reaching a specific diagnosis, the stage (degree of fibrosis) should be defined using the scoring system which is suitable for each pathology. When the histology does not translate into a conclusive diagnosis, the stage of the disease should be indicated through accurate descriptors, making the data usable for the clinician. Furthermore, an explanatory comment can be inserted on the diagnostic hypotheses reported if necessary.

TAT is a quality indicator defined as the time between acceptance of the sample and its reporting [9,10]. This time includes all stages of slide preparation, including fixation, cutting, and staining, and we propose it as an indicator of process quality when it does not exceed 10 working days in 75% of cases.

STEPS 6 AND 7. DIAGNOSIS AND THERAPY

The final diagnosis relies on the integration of clinical and histological data, which should be reinforced.

Therefore, the close interaction between the clinician and the pathologist working in the same hospital should be consolidated. Furthermore, a network should be established between liver pathologists and clinicians from different hospitals to discuss complex cases and seek a second opinion. From an innovative perspective, better integration between clinicians and pathologists could be incentivized throughout a platform for exchanging information and sharing complex cases to shorten the processing time.

Discussion

Given the importance that the biopsy examination has in many chronic liver diseases, the aim of our work was to outline a structured and standardized diagnostic process, to improve the diagnostic performance in terms of both accuracy and promptness of diagnosis.

The panel defined a process consisting of 7 phases from clinical and laboratory evaluation leading to therapy access. The first crucial issue is that the clinical suspicion should be sharp since the appropriateness of the biopsy examination relies on it. Currently, American and British guidelines recommend liver biopsy to establish the diagnosis and evaluate the staging of liver disease to direct management based on the underlying histology [6,11].

Table III. Sample description checklist.

Sample adequacy	
Architecture	Preserved, altered, or lost
Analysis of portal tracts	- description of ducts, arteries and veins - qualification, quantification and distribution of the inflammatory infiltrate - presence of fibrosis
Interface	Inflammatory, biliary, fibrous
Lobule	- organization: conserved or lost - necro-inflammatory infiltrate - type of necrosis (presence of apoptosis) - macrophage component: Kupffer cell hyperplasia/hypertrophy ceroid-laden macrophages, iron-laden Kupffer cells and macrophages, microgranulomas - sinusoids: dilatation and congestion
Hepatocyte evaluation	- steatosis: presence, quantification and distribution - presence and description of intracellular storage - morphology analysis: ballooning, feathery, groundglass, pseudo groundglass, biliary metaplasia - hepatocyte nuclei: anisokaryotic, binucleated, glycogenated nuclei
Fibrosis	Portal, periportal, bridging (porto-central/porto-portal/centro-central), perisinusoidal, perivenular
Terminal hepatic vein evaluation	Patent/obstructed
Bile	Presence or absence of bile in hepatocytes and resident macrophages; bile plugs in canaliculi and cholangioles
Comments	Insert, if necessary, an explanatory comment on the diagnostic hypotheses reported

It is essential that the clinical suspicion is clearly communicated to the pathologist performing the examination to ensure a proper flow of information. The panel proposes a standardized form, reporting the indication(s) along with all relevant clinical data, in line with international recommendations. This will ensure that the histopathologist has all the necessary information to conduct a thorough examination [6].

Another crucial aspect is the execution of the biopsy, which may require specialized centers, homogeneity of procedures and minimum quality standards in all its phases. Currently, there is limited data regarding biopsy quality that can guide clinicians' technical choices[11]. The size of the needle, the length of the samples taken, and the operator's skills are among the technical factors that have been shown to influence the diagnosis[3,11]. Based on the evidence from the literature, the panel defines an adequate biopsy sample as being non-fragmented and at least 20 mm in length. Additionally, for patients with widespread liver disease, the panel recommends using a needle with a diameter of 16-17 gauge for the procedure [2,6,11,12,13].

Finally, the interpretation and reporting phases require clarity, intelligibility, and usability. The published guidelines state that the report should adhere with the clinical indication(s) for the biopsy and conclude with a concise diagnostic summary [6]. Therefore, the panel proposes a descriptive checklist that contains the minimum diagnostic requirements, which constitutes a standard of quality and homogeneity and supports the pathologist in the reporting process.

The accuracy of all these phases allows a correct and timely diagnosis in order to ensure an appropriate therapeutic management. For this reason, it is advisable that for biopsies obtained outside a specialized liver center, the reporting pathologist should have access to a second opinion from a liver center[6,14].

A final point that covers the entire process is the expertise of the professional involved. Due to new non-invasive tools, the decrease in liver biopsy requests has led to a reduction not only in the number of biopsies performed but also in the professionals specialized in carrying out and interpreting these samples and examinations [15].

Conclusions

Sharing a standardized diagnostic path between the pathologist and the clinician can be a powerful tool to improve both the timing and accuracy of the histology report. This collaboration can also foster the growth of individual and collective knowledge. This can be con-sidered as a pilot project started with the involvement of only some sample regions and that we hope could spread nationally in the future.

AUTHORS' CONTRIBUTIONS

AB, DF FRP, GdA contributed equally to the drafting of the manuscript. All authors revised the manuscript and approved the final version.

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