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RESEARCH ARTICLE

UNEXPLAINED INTRAHEPATIC CHOLESTASIS: ROLE AND DIAGNOSTIC YIELD OF LIVER BIOPSY

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Abstract

Intrahepatic cholestasis represents a complex challenge for gastroenterologists due to its broad range of potential causes. Establishing an accurate diagnosis often requires extensive investigations and sophisticated tests, which are, in most cases, costly. Liver biopsy (LB) becomes necessary when noninvasive examinations fail to reveal an etiology.The aim of our study was to assess the diagnostic yield of LB in identifying the underlying causes of unexplained intrahepatic cholestasis.

Materials and Methods: We performed a retrospective descriptive study in the Department of Hepato-Gastroenterology at Hassan II University Hospital, Fez, Morocco, from January 1, 2017, to August 1, 2023. It included patients with chronic intrahepatic cholestasis lasting more than six months and with inconclusive initial workup (negative toxicology, normal ultrasound, negative viral serologies, and negative autoimmune markers) who underwent ultrasound-guided percutaneous liver biopsy. Data on demographics, clinical features, laboratory parameters, and histopathological findings were collected from medical records. Inconclusive cases were reviewed by a senior pathologist, and some underwent a second biopsy. Analysis was descriptive, reporting means, ranges, numbers, and percentages.

Results:A total of 29 cases were collected. The mean age was 41.8 years (range: 22–77 years), with a predominance of women (65.5%, n = 19). Clinical examination revealed jaundice in 5 cases (17%) and hepatomegaly in 2 cases (6.8%). Most cases (83%) presented with anicteric cholestasis.Biologically, total bilirubin levels ranged from normal values to up to 14 times the upper limit of normal (ULN). Cytolysis between 1.5 and 4 times the ULN was noted in 6 cases (20%).LB provided relevant diagnostic information in 11 cases (37.9%) from the first histopathological interpretation. It was initially inconclusive in 18 cases (62%). Among these, a diagnosis was established after re-review of the initial specimen in 3 cases, and after a second LB in 2 cases.The main diagnoses were primary biliary cholangitis (n = 8) and steatosis/steatohepatitis (n = 4). Other etiologies included granulomatous hepatitis (n = 3) and drug-induced liver injury (n = 1).In 13 patients (44.8%), LB did not yield a definitive diagnosis: normal hepatic parenchyma in 8 cases, nonspecific inflammatory remodeling in 5 cases, and nonspecific fibrosing hepatopathy in the remainder.

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Conclusion:In cases of chronic cholestasis without an identified etiology, LB remains an essential diagnostic tool, contributing to the diagnosis in more than one-third of our patients. However, its sensitivity depends greatly on the operator's technique and the pathologist's expertise.

Introduction:-

Unexplained intrahepatic cholestasis poses a significant diagnostic obstacle within the field of hepatology, attributable to the diverse spectrum of underlying etiologies and the restricted sensitivity of non-invasive diagnostic modalities. Although imaging techniques, serological evaluations, and biochemical analyses constitute vital initial investigative tools, these methods may inadequately elucidate the primary causeparticularly in cases of intricate or cholestatic liver pathologies.

Liver biopsy continues to be an essential instrument in such clinical scenarios. Histopathological evaluation not only aids in identifying specific disorders such as primary biliary cholangitis (PBC) in seronegative instances or overlap syndromes but also functions to stage the disease and inform therapeutic strategies. The most recent clinical guidelines acknowledge the significance of liver biopsy as particularly crucial when serological markers are either absent or ambiguous, and when imaging modalities fail to reveal significant bile duct abnormalities. [1]

Furthermore, in instances where drug-induced liver injury (DILI) is postulated, liver biopsy serves to enhance clinical evaluation by providing essential histological evidence. This procedure may assist in establishing drug-related causation, ruling out alternative conditions that may present similarly (e.g., autoimmune hepatitis), and informing therapeutic approaches, including the determination of whether to commence or defer immunosuppressive treatment.[1]

Extensive retrospective studies substantiate the role of liver biopsy in instances of hepatic dysfunction that are otherwise not elucidated. For instance, a contemporary cohort study conducted in China encompassing more than 1,300 subjects revealed that ultrasound-guided percutaneous liver biopsy effectively discerned prevalent etiologies—including viral hepatitis, neoplastic conditions, and drug-induced liver injury (DILI)—in a significant proportion of cases, whilst upholding an exceptional safety profile.[2]

The aim of our study was to evaluate the diagnostic contribution and yield of liver biopsy in determining the etiology of unexplained intrahepatic cholestasis in patients with inconclusive non-invasive investigations.

Methods:-

We conducted a retrospective descriptive study in the Department of Hepato-Gastroenterology at Hassan II University Hospital, Fez, Morocco, covering a period of six years and eight months, from January 1, 2017, to August 1, 2023. The study population included patients admitted for the evaluation of chronic intrahepatic cholestasis lasting more than six months, in whom the initial non-invasive assessment failed to determine the etiology. The baseline workup consisted of a detailed toxicological history, abdominal ultrasound, viral hepatitis serologies, and an autoimmune antibody panel. Only patients with a negative toxicology screen, negative viral serologies, and negative autoimmune markers were eligible for inclusion.

All included patients underwent an ultrasound-guided percutaneous liver biopsy (UG-PLB) performed by experienced hepatologists in the department, using standard aseptic technique and local anesthesia. The biopsy was carried out under real-time ultrasound guidance to ensure accurate targeting of the hepatic parenchyma and to minimize procedural risks. Specimens were immediately fixed in formalin and sent to the pathology laboratory for histological examination. Patients with incomplete medical records or with contraindications to liver biopsy, such as uncorrected coagulopathy, severe thrombocytopenia, extrahepatic biliary obstruction, or hemodynamic instability, were excluded from the study.

Data were collected retrospectively from patient medical files using a standardized data collection form. Variables analyzed included demographic data (age and sex), clinical features (presence or absence of jaundice, hepatomegaly, or other signs), biochemical parameters (total bilirubin, alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], and gamma-glutamyl transferase [GGT]), and histopathological findings. When the initial histopathological report was inconclusive, the biopsy specimen was re-examined by a senior

hepatopathologist. In selected cases, a second liver biopsy was performed to obtain additional diagnostic information.

The primary outcome measure was the diagnostic yield of liver biopsy, defined as the proportion of cases in which histopathology provided a specific etiological diagnosis. Secondary outcomes included the spectrum of histologically confirmed etiologies and the proportion of inconclusive results after initial and repeat biopsy.

Data analysis was descriptive. Continuous variables were summarized as means with ranges, and categorical variables as absolute numbers and percentages. Given the observational design and relatively small sample size, no inferential statistical analyses were performed.

Results:-

During the study period, 29 patients met the inclusion criteria for unexplained intrahepatic cholestasis and underwent ultrasound-guided percutaneous liver biopsy .The mean age at presentation was 41.8 years (range: 22–77 years), with a clear female predominance (65.5%, n = 19; male: 34.5%, n = 10).

Clinical Presentation:

The majority of patients (n = 24; 83%) presented with anicteric cholestasis. Clinically apparent jaundice was documented in 5 cases (17%), while hepatomegaly was noted in 2 patients (6.8%). No patient presented with splenomegaly or clinical signs of advanced liver disease at the time of biopsy. Pruritus was reported in 4 cases (13.8%), all of which were associated with cholestatic biochemical profiles.

Laboratory Findings:

Biochemical analyses revealed a wide range of cholestatic patterns. Total bilirubin levels varied from within the normal range to as high as 14× the upper limit of normal (ULN). Six patients (20%) showed associated cytolysis, with alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels between 1.5 and 4× ULN. Alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) were elevated in all cases, with mean values corresponding to 3.8× and 5.1× ULN, respectively. Synthetic liver function (albumin, prothrombin time) was preserved in all patients.

Histopathological Findings:

The first histopathological interpretation of the liver biopsy specimen yielded a specific etiological diagnosis in 11 patients (37.9%). Among these, the most frequent condition was primary biliary cholangitis (PBC) (5 cases; 17.2%), followed by steatosis or steatohepatitis (3 cases; 10.3%), granulomatous hepatitis (2 cases; 6.9%), and drug-induced liver injury (DILI) (1 case; 3.4%).

In 18 patients (62.1%), the initial histopathological report was inconclusive. A second review of the original specimen by a senior hepatopathologist established a diagnosis in 3 additional patients (2 PBC, 1 steatosis/steatohepatitis), and a second liver biopsy provided a diagnosis in 2 further cases (1 PBC, 1 granulomatous hepatitis). This re-evaluation process increased the overall diagnostic yield to 16 patients (55.2%), including 8 PBC (27.6%), 4 steatosis/steatohepatitis (13.8%), 3 granulomatous hepatitis (10.3%), and 1 DILI (3.4%).

Non-Diagnostic Biopsies:

Thirteen patients (44.8%) remained without a specific histological diagnosis after all evaluations. Among them, 8 showed normal hepatic parenchyma, 5 displayed nonspecific inflammatory remodeling, and a minority presented nonspecific fibrosing hepatopathy without distinctive features suggestive of a defined etiology.

Diagnostic Yield and Safety:

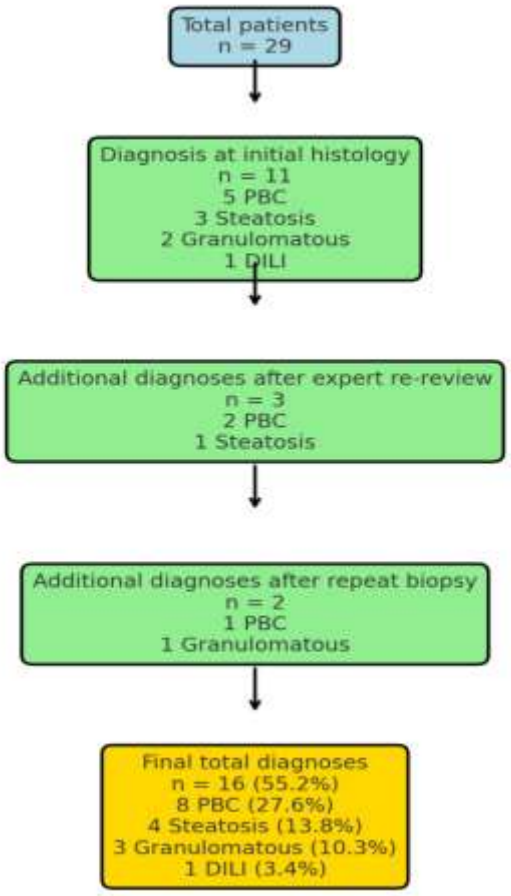
The final diagnostic yield of UG-PLB in this cohort was 55.2%, meaning that more than half of patients with unexplained cholestasis benefited from a histologically confirmed etiology. No major complications were recorded. Minor post-procedural pain occurred in 5 patients (17.2%), managed with simple analgesics, and no post-biopsy bleeding or infection was observed.

The main demographic, clinical, biochemical, and histopathological characteristics of the 29 patients included in the study are summarized in Table 1.

Category	Results
Number of patients	29
Age, mean (range), years	41.8 (22–77)
Sex ratio (F/M)	19/10
Jaundice, n (%)	5 (17.2%)
Hepatomegaly, n (%)	2 (6.8%)
Anictericcholestasis, n (%)	24 (83%)
Pruritus, n (%)	4 (13.8%)
Total bilirubin range	Normal – 14× ULN
Cytolysis (ALT/AST 1.5–4× ULN), n (%)	6 (20%)
ALP mean × ULN	3.8
GGT mean × ULN	5.1
Preservedsyntheticfunction, n (%)	29 (100%)
Primarybiliarycholangitis, n (%)	8 (27.6 %)
Steatosis/steatohepatitis, n (%)	4 (13.8 %)
Granulomatoushepatitis, n (%)	3 (10.3 %)
Drug-induced liver injury, n (%)	1 (3.4 %)
Normal parenchyma, n (%)	8 (27.6%)
Nonspecificinflammatoryremodeling, n (%)	5 (17.2%)
Final diagnostic yield (%)	55.2%
Minor complications (post-biopsy pain), n (%)	5 (17.2%)
Major complications	None

The stepwise diagnostic yield of ultrasound-guided liver biopsy in the evaluation of unexplained intrahepatic cholestasis is shown in Figure 1, highlighting the number of diagnoses obtained at each stage and the proportion of patients remaining without a definitive diagnosis.

Figure 1. Stepwise diagnostic yield of ultrasound-guided liver biopsy in unexplained intrahepatic cholestasis



Discussion:-

Diagnostic yield and comparison with the literature:

The diagnostic yield of 55.2% in our cohort is lower than the rates commonly reported for ultrasound-guided percutaneous liver biopsy performed for unexplained abnormal liver tests, where yields around 85–87% have been described [5]. Several factors likely explain this difference in our setting. First, our study deliberately targeted patients with stringently defined "unexplained" intrahepatic cholestasis, thereby excluding clinically obvious diagnoses that would have inflated yield in broader series [5], [6].

Second, specimen adequacy including core length and the number of portal tracts has a well-recognized impact on histologic performance, and suboptimal samples can depress yield [7]. Third, heterogeneous or patchy diseases may benefit from bilobar sampling, which was not systematic in our series [7]. Finally, the initially inconclusive interpretations in 18 patients (62.1%) but five additional diagnoses after expert re-review and selective re-biopsy underscore the decisive contribution of experienced hepatopathology and structured re-evaluation pathways to maximize yield [7], [8].

Demographic profile and clinicalpresentation:

The female predominance (65.5%) aligns with the epidemiology of autoimmune cholestatic liver diseases, particularly primary biliary cholangitis (PBC), which affects mainly middle-aged women [9], [10]. The predominance of anicteric cholestasis (83%) is clinically meaningful and suggests earlier disease detection prior to overt jaundice [11], effective biochemical surveillance capable of identifying subclinical cholestasis, and a presentation consistent with moderate forms of PBC and other chronic cholangiopathies [10], [12]. The absence of splenomegaly or signs of advanced liver disease further indicates that most patients were assessed at a relatively early stage [13].

Biochemical profile and histopathologiccorrelations:

A cholestatic pattern characterized by elevated alkaline phosphatase (mean 3.8× ULN) and GGT (mean 5.1× ULN) with preserved synthetic function is typical of chronic cholestasis without hepatocellular failure [14], [15]. A moderate cytolysis (ALT/AST 1.5–4× ULN) in 20% of cases may reflect PBC–AIH overlap syndromes [16], cholestatic processes with a concurrent hepatocellular inflammatory component [8], or drug-related or metabolic injury in selected patients [17].

Histopathology: criticalanalysis of diagnoses:

Primary biliary cholangitis (PBC) accounted for 27.6%of diagnoses consistent with its frequency among series of unexplained cholestasis [10], [18]. This emphasizes the role of biopsy in: (i) confirming PBC when serology is atypical or AMA-negative ([10], [19]); (ii) providing staging and prognostic assessment (including sinusoidal and portal fibrosis, which carry independent prognostic value) [8], [20]; and (iii) differentiating PBC from other chronic cholangiopathies [21].

Steatosis/steatohepatitis (13.8%) reflects the frequent co-occurrence of metabolic syndrome in patients with cholestatic profiles [22] and the possibility that MASH itself can present with cholestasis, especially in advanced disease [23]; careful metabolic context appraisal is integral to evaluating cholestatic abnormalities [24].
Granulomatous hepatitis (10.3%) mandates a systematic work-up to exclude infection (e.g., tuberculosis, histoplasmosis) [25], hepatic sarcoidosis [26], drug reactions [27], and PBC with granulomatous features [28].

Procedural safety and comparison with benchmark data:

The excellent safety profile observed (0% major complications; 17.2% minor, self-limited pain) is in line with contemporary data for ultrasound-guided percutaneous biopsy [29], [30]. Comparative studies show similar complication rates between percutaneous ultrasound-guided biopsy and EUS-guided liver biopsy (EUS-LB) [31], [32]. Ultrasound guidance improves safety relative to historical "blind" approaches [33], and major complications such as hemorrhage or pneumothorax remain rare (<1–2%) when modern, guided techniques are used [34].

Re-evaluation strategy and optimization of diagnostic yield:

The rise in yield from 37.9% to 55.2% after expert pathology re-review and selective re-biopsy highlights three key levers for optimization: routine second-look review by an experienced hepatopathologist [7], [8]; rigorous clinicopathologic correlation when interpreting indeterminate features [35]; and ongoing training in hepatopathology to maintain high interpretive standards [36]. Re-biopsy proved valuable in two additional cases in our series,

supporting its use when there is persistent clinical suspicion [37], technical inadequacy of the first sample [38], or unexplained clinical/biochemical evolution despite an initially non-diagnostic biopsy [39].

Clinical and therapeutic implications:
Achieving a specific histologic diagnosis in 55.2% of patients likely enabled: initiation of disease-directed therapy (e.g., ursodeoxycholic acid for PBC) [40]; withdrawal of hepatotoxic agents in suspected/confirmed DILI [41]; appropriate surveillance and genetic counseling when indicated [42]; and better prognostic stratification and follow-up planning [43].

For the 44.8% without a definitive histologic diagnosis, we advocate regular clinical and biochemical follow-up [44], periodic re-evaluation with complementary tests as indicated [45], and consideration of alternative diagnostic modalities including MRCP and, where appropriate, genetic testing to refine the differential [46].

Limitations and perspectives:
Key limitations include the modest sample size (n=29) [47], the absence of systematic correlation with non-invasive tests (elastography, serum biomarkers) that might have added granularity [48], and the lack of long-term outcome data to quantify prognostic impact [49].

Future directions include integrating molecular and advanced immunohistochemistry panels to refine etiologic attribution [50]; exploring artificial intelligence assisted histology to reduce indeterminate reads [51]; and developing predictive scores to optimize patient selection for biopsy in unexplained cholestasis [52].

Comparison with alternative diagnostic strategies:
Among non-invasive tools, transient elastography correlates well with fibrosis in PBC and may reduce the need for biopsy in staging scenarios [53]. Serologic biomarker panels (e.g., ELF, FibroTest) can further decrease biopsy utilization in selected contexts [54].

MRI with cholangiography can identify certain cholangiopathies without tissue sampling [55]. Nonetheless, EUS-LB is a viable alternative with comparable diagnostic yield to percutaneous biopsy [56], the option of systematic bilobar sampling [57], and a similar safety profile in experienced hands [58]. In patients already undergoing endoscopy or with unfavorable percutaneous windows, EUS-LB represents a pragmatic choice.

Conclusion:-

Ultrasound-guided percutaneous liver biopsy persists as a significant and secure diagnostic modality for cases of unexplained intrahepatic cholestasis. Within our studied population, it attained a commendable diagnostic yield of 55.2%, accompanied by an exceptional safety profile.

The diagnostic efficacy is optimized when specimens are assessed by proficient hepatopathologists, when the selective repetition of the biopsy is contemplated for cases that remain persistently unexplained, and when the integration of clinicopathologic correlation amalgamates clinical, biochemical, imaging, and histological data within a multidisciplinary context.

Diligent patient selection—anchored in comprehensive clinical and paraclinical evaluation prior to biopsy—further enhances diagnostic yield while mitigating the incidence of unnecessary interventions. Ultimately, systematic long-term follow-up is imperative to evaluate the prognostic ramifications of diagnoses established via biopsy and to identify conditions that may manifest over time.

These findings support the continued use of UG-PLB in selected patients with unexplained intrahepatic cholestasis, particularly when interpreted by expert hepatopathologists and complemented by selective re-biopsy strategies. Future efforts should focus on integrating non-invasive tools, molecular diagnostics, and multidisciplinary review to further enhance diagnostic accuracy and guide individualized patient management.

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