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Original Article

Are there inflammatory changes in the hepatic biopsies of patients with acute cholangitis of lithiasic origin?

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Abstract

Introduction: **Acute cholangitis (AC) is a clinical diagnosis entity. A high prevalence of acute inflammatory changes (AIC) are found in hepatic needle biopsies (HB) in these patients. The aim of our study is to determine the prevalence of AIC in HB performed on patients with AC due to biliary stones.** ***Methods:*** **Cross-sectional study. Surgery was performed at the Hospital Regional of Temuco. Patients with Charcot's triad, over 15 years of age, and surgical exploration of common bile duct were included. There was exclusion if periampullary tumor or liver cirrhosis was suspected. Bile macroscopy and hepatic histopathology were determined. A hepatic needle biopsy was taken during surgery. Biopsies were analyzed by two independent pathologist groups and kappa statistics were applied.** ***Results:*** **From January to June, 2002, fifty-three patients (83% female) with a median age of 60.7 years with AC were operated on. We found 83% with pus in the biliary system and 17% with cloudy bile. Histopathology: minimal changes (32%), hepatic steatosis (25%), chronic periportal infiltration (17%), liver cirrhosis (11%), AIC (6%) and normal (9%). Kappa statistics were 0.77. In conclusion a low prevalence of AIC was found in the HB of patients with AC.**

Key words: Common bile duct calculi[Multi], "Cholangitis" [MeSH], "Biopsy, Fine-Needle"[MeSH], "Pathology, Surgical"[MeSH], "Choledocholithiasis" [MeSH], "Common Bile Duct Diseases" [MeSH], "Prevalence" [MeSH].

Cholangitis means inflammation of the bile ducts.[1] In the 1980s, a theory existed that acute cholangitis (AC) presented a clinical spectrum that varied from a slight form called AC or ascending, which presented Charcot's triad and was caused by a bacterial infection of the biliary tree without finding any pus in the exploration of the biliary duct, up to suppurative cholangitis, which was clinically defined by Reynold's pentad and was associated with pus in the exploration of the bile duct and corresponded to the most serious expression of the pathology.[2]

Although Charcot's triad is currently the gold standard in the diagnosis of cholangitis, this manifests in approximately 60% of the cases, according to various publications.[3,4] These numbers are insufficient for it to be the gold standard of such a prevalent pathology.[2] In the search for a better gold standard, we contemplated hepatic biopsy which, although it does not help us in normal daily clinical practice, can be useful to interpret and investigate future diagnostic tests with better results than Charcot's triad. However, it has been verified in previous studies that in patients with acute biliary obstruction, the hepatic histology can be normal or have no correlation at all to the clinical symptoms.[4-8]

The hypothesis of our study is that there is a high prevalence of inflammatory changes in the hepatic biopsies of patients with acute cholangitis of lithiasic origin. The objective of this study is to determine the prevalence of acute inflammatory changes (AIC) in hepatic needle biopsies (BH) obtained through surgical intervention from patients with AC of lithiasic origin.

Materials and methods

A cross-sectional study of histological material was conducted, taken from patients with a clinical impression of AC.

Patients included were older than 15 years of age, with Charcot's triad on entering the ER, operated on (open exploration of the biliary duct) and who were willing to participate in the study (in cases of changes

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in a state of consciousness, acceptance and consent was obtained from the closest responsible family member).

The professional that recruited the patients was masked with respect to the application of the test under study. Subjects with preoperative endoscopic exploration of the biliary duct, neurological deterioration not attributable to the symptoms of sepsis of biliary origin, documentation of neoplasia of the liver and biliary ducts and hepatic macroscopy compatible with chronic liver damage were excluded.

For the selection of cases, a nonprobabilistic sample of consecutive patients was applied. The patients were operated on using the incision preferred by the surgeon. Once the hepatoduodenal ligament had been dissected and the common bile duct identified, a longitudinal choledocotomy was performed with stone extraction, an intraoperative cholangiography to prove adequate distal permeability and a choledocoraphy on the Kehr tube. Once the exploration of the biliary duct was complete, a needle HB was carried out (Tru-Cut®) on a random part of segment IVb, with an average depth of 5 cm. Immediately afterwards, the samples obtained were placed in individual labeled jars with 10% formalin. The specimens were prepared according to conventional techniques on paraffin blocks and the histological slides stained with hematoxiline-eosine were interpreted by two independent groups of general surgical pathologists, two for each group. The pathologists were masked at all times respect to patient‘s diagnosis. If there was disagreement the diagnosis was reached by consensus by concurrence of both groups of pathologists.

With a foundation in the revision of the literature[1,3,5] and in the consensus of the groups of pathologists that participated in the study, the definition of polymorphonuclear infiltration in the periportal spaces was adopted as AIC and as minimal changes, cellular tumefaction or minimal periportal fibrosis that was considered temporary or reversible.

The size of the sample considering a prevalence of hepatic histological changes in patients with AC was calculated at 80,[3,5,9] a reliability level of 95% and accepting a minimum prevalence of AIC in HB in patients with AC at 70%. Thus, a minimum sample was obtained for the performance of the study of 53 patients.

An exploratory analysis of the data was conducted. Descriptive statistics were used with a calculation of the measures of central tendency, dispersion and extreme tendency.[10] Interobserver reliability was determined using Kappa statistics, and the prevalence of AIC was also determined. Data were analyzed using Stata® 8.0.

The protocol was approved by the Ethics Committee of the Faculty of Medicine at the Universidad de La Frontera. The data obtained were codified in such a way as to ensure participant confidentiality.

Results

The sample studied was composed of 65 patients, 83% women, with an average age of 60.7 years (24 - 79 years of age).

Pus in the biliary system was verified through biliary macroscopy in 83% of the cases and cloudy bile in 17% of the cases.

The degree of concurrence among the pathologists in the final diagnosis of hepatic histology was 85%, with a Kappa of 0.77.

The prevalence of AIC in HB was 6%. The rest of the histopathological findings were: minimal changes (32%), hepatic steatosis (25%), chronic periportal infiltration (17%), liver cirrhosis (11%), AIC (6%) and normal (9%).

There were no complications associated with the performance of the biopsy.

Discussion

When we speak of AC, we all imagine a patient presenting with Charcot’s triad. Nevertheless, as surgeons, we know that there is a not inconsiderable number of patients who, having AC, do not express it in this way, manifesting an incomplete syndrome.[11] Such is the case in those immunodepressed patients that present no fever due to their underlying condition (Diabetes Mellitus, HIV) or even cholangitis (sepsis, MODS). Moreover, there are those patients that clinically are quite well but present pus when the common bile duct is opened. Therefore, there is one simple question, which has a very complex answer: what is AC? In the search for an answer, we thought of a diagnostic test such as the HB, since traditionally histopathology has been thought of as the gold standard for diagnosing hepatic diseases. However, our results and the existing literature do not totally support this theory[7,8] in the sense that there is no association between the clinical symptoms (Charcot’s triad) and the hepatic histopathology. In attempting to understand the reason for this dissociation, which does not seem logical if consider the current physiopathological model of AC that incorporates hepatocellular and canalicular damage as the axis central to the initial injury, we must assess whether HB should be considered or not as a gold standard for this pathology in particular.

The aspects that we need to consider in analyzing HB are the same as those applied to any diagnostic test: the sampling, the taking of the sample (technique) and the reporting of the result.[12]

The sampling of large organs has been widely discussed in other publications.[12-14] A liver sample taken by Tru-Cut® measures approximately 1 to 3 cm in length with a diameter of 2mm. This represents 1/50,000 of the total of the hepatic mass.[13] What, then, is the necessary number of samples to be taken to obtain a value representative of the liver? The answer to this depends on whether

we are confronted with a diffuse disease of the liver or a particular lesion. For diffuse lesions of the liver such as AC, a sample delivered by any of the existing mechanisms is considered appropriate,[13] whereas for hepatic focal lesions, the best output is obtained with the support of images (echography, CT) in such a way as to conduct directed biopsies.[13] Therefore, in this study, the problem of sampling was resolved.

In relation to the taking of the sample, it is worth noting that this is related to the technique used. It would be problematic if our study were based on a series of retrospective cases, but by using a cross-sectional design, this is overcome. The protocol for sample-taking was evaluated prior to conducting the study with the aim of reducing bias in this respect. The samples were similar with regard to quality and size.

On the other hand, the HB report is not exempt from debate owing to the great interobserver variability that has been reported.[12,14-16] It has been stated that the biopsy report should be so standardized as to consist of a revising system that leaves no room for personal interpretation. The histopathology report can contain only 50% of what is clinically required for one pathology in particular.[16,17] In our case, this point was worked through specifically so that in both the reading and the reporting, the results were standardized. The result of this is the excellent performance that both groups of pathologists show, with their reports coinciding in 85% of the patients (almost perfect kappa).[18] The degree of concurrence obtained is considered good, which internally validates the results of the study.

What we have touched upon demonstrates that the HB is not a good gold standard in the diagnosis of AC. The histopathological changes associated with AC in our series were 6% and could reach 38% in the best-case scenario were we to accept the inclusion of minimal changes such as an added histopathological event. This makes us think that if the HB is not a good diagnostic indicator of AC, this would not be an illness whose primary expression is hepatic but rather that the signs and symptoms of AC could be attributed to other factors that have not as yet been defined, such as mediators of inflammation (cytokines and complement cascade), the patient's immune response (leukocytary response, autoregulatory mechanisms of inflammation) or germ characteristics (bacterial strain, microbial resistance, virulence).[19,20]

Lastly, the prevalence of almost one third of chronic inflammatory changes in livers with normal macroscopy is noteworthy. The existence of data related to our results was widely sought, but not one reference was found.

In summary, we can conclude that a low prevalence of AIC was found using HB in surgically intervened patients with AC, with a substantial interobserver reliability for histopathological diagnosis.

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