

FREQUENCY AND PREDICTIVE FACTORS OF GRANULOMATOUS HEPATITIS IN PATIENTS WITH PERITONEAL TUBERCULOSIS

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FREQUENCE ET FACTEURS PREDICTIFS DE L'HEPATITE GRANULOMATEUSE AU COURS DE LA TUBERCULOSE PERITONEALE

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RÉSUMÉ

Buts : déterminer la fréquence de l'hépatite granulomateuse chez les patients ayant une tuberculose péritonéale, identifier les facteurs de haut risque de l'atteinte hépatique tuberculeuse et déterminer si celle-ci est associée à un risque plus important d'apparition d'effets indésirables du traitement antituberculeux.

Methods: nous avons mené une étude prospective colligeant les patients atteints d'une tuberculose péritonéale confirmée histologiquement entre Janvier 1996 et Décembre 2005. Une ponction biopsie du foie a été réalisée avant l'initiation du traitement anti-tuberculeux à la recherche systématique d'une hépatite granulomateuse.

Résultats: 52 patients ont été colligés, 9 hommes et 43 femmes d'âge moyen de 35,5 ans. Une hépatite granulomateuse a été observée chez 24 patients (46%). En analyse univariée, les facteurs associés à un risque élevé d'atteinte hépatique sont un taux plus élevé de gamma glutamyl transférase (44.5 + 36.8 IU/l vs 23.3 + 9.28 IU/l p = 0.005), un taux plus élevé de phosphatases alcalines (233.9 + 96.6 IU/l vs 189.4 + 49.9 IU/l p = 0.03) et un taux plus bas de cholestérol (1.22 + 0.2 g/l vs 1.56 + 0.3 g/l p < 0.0001). En analyse multivariée seul un taux de cholestérol inférieur à 1,31 g/l est significativement associé à la présence d'une hépatite granulomateuse (p = 0.006 OR [IC95%] : 0.10 [0.02 - 0.52]).

Conclusion: nous avons retrouvé une atteinte hépatique fréquente au cours de la tuberculose péritonéale (46%). Un taux de cholestérol inférieur à 1,31 gr/l est un facteur prédictif indépendant de la présence d'une hépatite granulomateuse. Dans ce cas, une ponction biopsie hépatique percutanée pourrait constituer une alternative à la coelioscopie diagnostique.

SUMMARY

Aims : The aims of our study were to determine the frequency of granulomatous hepatitis in patients with peritoneal tuberculosis, to identify factors for high risk and whether it is associated with higher frequency of antituberculous treatment side effects.

Methods: We carried out a prospective study on patients with histologically proven peritoneal tuberculosis between January 1996 and December 2005. We performed a liver biopsy in all the patients before starting the antituberculous treatment. Granulomatous hepatitis was systematically searched in all patients.

Results: The study was conducted in 52 patients, 9 men and 43 women of median age of 35.5 years. A granulomatous hepatitis was seen in 24 patients (46%). In univariate analysis the factors associated with a high risk of liver involvement were a higher level of gamma-glutamyl transpeptidase (44.5 + 36.8 IU/l vs 23.3 + 9.28 IU/l p = 0.005), a higher level of phosphatases alkalines (233.9 + 96.6 IU/l vs 189.4 + 49.9 IU/l p = 0.03) and a lower level of cholesterol (1.22 + 0.2 g/l vs 1.56 + 0.3 g/l p < 0.0001). In multivariate analysis, only a cholesterol level lower than 1,31 g/l was significantly associated with a granulomatous hepatitis (p = 0.006 OR [IC95%] : 0.10 [0.02 - 0.52]).

Conclusion: We have found a frequent liver involvement in the case of peritoneal tuberculosis (46%). Cholesterol level lower than 1,31gr/l was an independent predictor of granulomatous hepatitis in patients with peritoneal tuberculosis. We suggest, in this case, that percutaneous liver biopsy can be considered as an alternative to laparoscopy.

MOTS - CLÉS

Hépatite granulomateuse - Tuberculose péritonéale

KEY - WORDS

Peritoneal tuberculosis - Granulomatous hepatitis

تواتر وعوامل إنذار التهاب الكبد أثناء الإصابة بمرض السل في الصفاق

الباحثون : ن.بن مصطفى.س.قروي.م.سرغيني.ل.قال.أ.مكني.ف.شابي

الهدف من هذه الدراسة هو تحديد تواتر التهاب الكبد الجيومي عند المرضى المصابين بمرض السل في الصفاق أشتملت دراستنا على 52 حالة وقع تجميعها خلال 10 سنوات (1996-2005) بعد إجراء عملية خزع على مستوى الكبد عند كل المرضى كانت النتيجة أن 24 مريضة (46 %) كانوا مصابين بالتهاب في الكبد نستنتج أن الإصابة بالتهاب الكبد متواجدة بكثرة عند المرضى المصابين بمرض السل في الصفاق لذلك إن عملية الخزع في الكبد عبر الجلد تمثل طريقة معوضة للتنظير.

الكلمات الأساسية : التهاب الكبد الجيومي - سل في الصفاق

The incidence of tuberculosis is increasing in western countries during the last decades because of population migrations and immunodepression related to HIV infection and alcoholic cirrhosis [1]. In Tunisia, tuberculosis is an endemic disease with an estimated prevalence of 20.1 cases/100000 inhabitants according to the Tunisian healthcare database published in 2006. It affects the lung with a high predilection, because of the tubercule bacilli properties, Extra-pulmonary forms of tuberculosis which account for 10-15 per cent of all cases may represent up to 50 per cent of patients with AIDS [2].

The peritoneum can be involved in 4 to 10% cases of extra-pulmonary tuberculosis [3], and being the only patent disease at presentation but this doesn't exclude the possible involvement of other organs, which may have an impact on the treatment drugs and period. That's why a systematic check should be done to identify other organs affected by this infectious disease such as: lung, liver, urinary tract and gut.

Few data are available regarding peritoneal tuberculosis and no data are available regarding the frequency of such involvements particularly of the liver. That's why we conducted in our unit a prospective study which aims were to determine the frequency of granulomatous hepatitis in patients with peritoneal tuberculosis, to identify its risk factors and whether it is associated with higher frequency of antituberculous treatment side effects.

PATIENTS AND METHODS

1- Patients

We conducted a prospective study from January 2000 through December 2006.

Inclusion criteria: patients were eligible if they have a confirmed histologically peritoneal tuberculosis by peritoneal biopsies per laparoscopy or by pleural biopsies if it was an associated pleuretic fluid at presentation.

Exclusion criteria : altered hemostatic tests, treatment started before having diagnostic confirmation.

2- Methods

Liver biopsies were performed either by the surgeons at the time of peritoneal laparoscopy or by the gastroenterologist in our unit percutaneously after diagnosis of peritoneal tuberculosis was made, in the case of no contra-indications.

All the specimens were studied by the same pathologist. The pathologist has to check for the presence of granuloma which is recognised by a focal accumulations of modified macrophages (epithelioid cells), which may fuse to form multinucleated giant cells, and typically have a surrounding rim of lymphocytes and fibroblasts giving so the evidence of liver tuberculosis. The presence of caseum is not necessary for the diagnostic in this context.

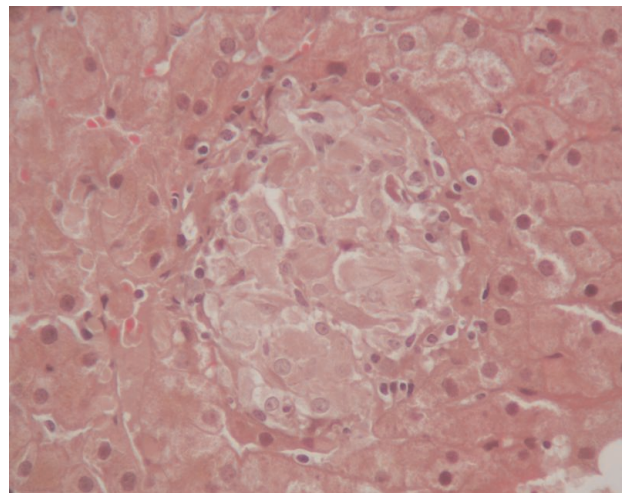
(figure 1).

3- Statistical analysis

Data keyboarding and analysis of the results were performed by SPSS11.0 software. The comparison of quantitative values was performed by the Student's t test. The qualitative values were

compared by the chi-square test or Fisher's exact test. The multivariate analysis was performed by a stepwise multiple linear regression model. The association between the quantitative variables was calculated by the Spearman coefficient of correlation (r). The optimal cut-off value calculated using the ROC curve. P values were considered statistically significant if less than or equal to 0.05.

Figure 1 : Hepatic granuloma (Liver histopathology. HE x 500).



RESULTS

1- Patients characteristics

Between January 2000 and December 2006, a diagnosis of peritoneal tuberculosis was carried in 81 patients. We include in the study 52 patients for whom a liver biopsy was carried out.

They were 43 women and 9 men, of median age: 35,5 years. All patients had at presentation an exudative ascetic fluid (albumin level higher than 30 gr/l) with a high white cell count (over 400 WC/mL, lymphocytes typically predominate).

The diagnosis of peritoneal tuberculosis was confirmed histologically in all cases. Biopsies were done by laparoscopy in 50 cases and by pleural biopsy in 2 cases.

Liver biopsies were performed by the surgeon in 28 cases and by the gastroenterologist in 24 cases.

2- Frequency and predictive factors of a granulomatous hepatitis

a- Frequency

Hepatic granuloma were seen in 24 patients (48%).

b- Predictive factors:

Univariate analysis

No significant clinical factor (age and sexe) was significantly associated with the existence of hepatic granuloma (Table 1).

When considering the absolute value of each biologic factors , higher levels of GGT(23,3 + 9,2 vs 44,5 + 36,8, p=0,005) and

PL (189,4 + 49,9 vs 233,9 + 96,6 p=0,03) and lower Cholesterol level (1,5 + 0,3 vs 1,2 + 0,2 p<0,0001) were significantly associated with the presence of hepatic granuloma.

Using the ROC curves, we were able to determine the Threshold value which is associated with the higher sensitivity and specificity (Table 2)

Table 1 : univariate analysis for the presence of liver tuberculosis

Variable	Granulomatous hepatitis present	Granulomatous hepatitis absent	P
Sexe (M/F)	4/20	5/23	0,6
Age (years)	34,8	35,7	0,55
AST (IU/L)	29,7 + 20	24,3 + 10,4	0,45
ALT (IU/L)	22,4 + 10,8	19,4 + 10,9	0,52
GGT (IU/L)	44,5 + 36,8	23,3 + 9,2	0,005
PL (IU/L)	233,9 + 96,6	189,4 + 49,9	0,03
BIL (mg/l)	5,9 + 2,9	4,9 + 4,7	0,26
CHOL (g/l)	1,2 + 0,2	1,5 + 0,3	< 0,0001
ALB (g/l)	26,9 + 6,5	29,5 + 7,1	0,16

ALT: alanine aminotransferase, AST : aspartate aminotransferase, AP : alkaline phosphatase GGT :gamma-glutamyltranspeptidase, BIL : bilirubin, CHOL : cholesterol, ALB : albumin, IDR : tuberculin interdermal reaction.

Table 2 : Threshold values associated with the higher sensitivity and specificity

	Threshold value	Se (%)	Sp (%)
GGT (IU/L)	19	91,7	51,1
PAL (IU/L)	208	70,8	71,4
CHOL (g/L)	1,31	87,5	75

Multivariate analysis

Only a cholesterol level lower than 1,31 gr/l was an independent predictor for the presence of granulomatous hepatitis (p = 0,006 adjusted OR [IC 95%]: 0,1 [0,02-0,52]) When Cholesterol is lower than 1,31gr/l; 83% of patients have granulomatous hepatitis.

3- Response to the treatment and side effects:

All patients were started on quadruple antituberculous therapy comprising rifampicin (10 mg/kg·d), isoniazid (5 mg/kg·d), pyrazinamide (30 mg/kg·d) and ethambutol (15 mg/kg·d) or streptomycin (15 mg/kg·d, maximum 1g.d) for two months and then maintained on rifampicin and isoniazid for 9 to 12 months. outcome was favourable in all patients. The clinical condition (weight, temperature, physical examination) was assessed at two and six months of treatment. Abdominal ultrasound was done systematically at the end of the treatment.

Moreover, side effects were not more frequent in case of granulomatous hepatitis. We have recorded increased levels of liver tests in 11 cases (6 HG+, 5HG- p = NS), there wasn't also a difference in patients without side effects according to the presence or the absence of granulomatous hepatitis (42 cases : 22HG+, 19 HG-).

DISCUSSION

Tuberculosis causes some 3 million deaths per year world wide and is increasing in incidence in industrialized and developing countries. Abdominal TB, which may involve the gastrointestinal tract, peritoneum, lymph nodes or solid viscera, constitutes up to 12% of extrapulmonary TB and 1-3% of the total [2,4]. Both the incidence and the severity of abdominal tuberculosis are expected to increase with increasing incidence of HIV infection and use of anti-TNF therapy. It's still endemic in many countries.

Peritoneal involvement may occur from spread from lymph nodes, intestinal lesions or from tubercular salpingitis in women. Abdominal lymph nodal and peritoneal tuberculosis may occur without gastrointestinal involvement in about one third of the cases, other solid organs can be involved especially the liver and the spleen [5]. Peritoneal tuberculosis occurs in three forms: wet type with ascitis, dry type with adhesions, and fibrotic type with omental thickening and loculated ascites. In our study all patients diagnosed have ascites.

Abdominal tuberculosis is predominantly a disease of young adults. Two-thirds of the patients are 21-40 yr old and the sex incidence is equal, although some studies have suggested a slight female predominance which is concordant with our findings [6].

Because the disease is insidious, symptoms of peritoneal tuberculosis are generally of lengthy delay before hospital admission, ranging from 1 to 14 months, in our study, this delay was about 7 months.

Peritoneal tuberculosis requires rapid diagnostic confirmation, to exclude carcinomatosis which is the main differential diagnosis, and to start appropriate treatment. Culture of the ascetic fluid is largely unhelpful; its result is available usually 2 months later and is positive in a minority of patients [7]. For this reason, all of our patients have a histological cofirmation of the disease, and so laparoscopy was carried out for the majority. To date little is knew about liver involvement in the course of peritoneal tuberculosis, its impact on outcome and occurrence of side effects is unknown.

In the literature, there are few studies about peritoneal tuberculosis which are retrospective - except the one of Bedioui and al- including usually a small number of patients. Frequency of liver involvement was available in four studies, ranging from 9 to 46% [7 – 10].

In this study we have found that liver is involved in patients with peritoneal hepatitis in 46% of cases. This frequency is concordant with another single study [7]. We have also studied for the first time, predictors for the presence of granulomatous hepatitis. We have found that a cholesterol level lower than 1,31 gr/l was an independent positive predictor of granulomatous hepatitis associated with a peritoneal tuberculosis. The significance of this finding isn't clear.

In our study we have demonstrated, for the first time that granulomatous hepatitis has no impact on response to antituberculous treatment and more over, we have not recorded a higher frequency of side effects (cytolysse or other side effects) in this case.

On the other hand, epithelioid granulomas have been reported in 2–15% of unselected liver biopsies, with numerous underlying aetiologies described [11-15]. However, the majority of these series were reported before identification of hepatitis C virus, now recognised as a common cause of hepatic epithelioid granulomas. It is typically said that hepatic granulomas most often occur in the course of sarcoidosis or tuberculosis, but they also occur in other infectious diseases (bacterial, viral, fungal), inflammatory systemic diseases (collagenous disease, inflammatory bowel disease), neoplasia (gastrointestinal carcinoma and lymphoma), some drugs are also implicated in hepatic granulomas (allopurinol, penicillin...). In the literature few histopathologic studies have investigated the frequency of the tuberculous origin in hepatic granulomas. It was for about 1,8% in Europe [12], 21% in South Africa [16] and 4,8% in the United Kingdom [17], but no predictor factors were researched for. Moreover, liver biopsy in case of peritoneal tuberculosis is not agreed on by all the authors, for some, this is associated with

certain morbidity and liver involvement do not change therapeutic strategy. Although Laparoscopy is the method of choice with nearly zero mortality and very low morbidity, but is nevertheless a surgical operation with the real inherent risks of anesthesia and surgery. Our study shows that in patients with a probable tuberculous ascitis and a cholesterol level lower than 1,31 gr/l, hepatic granulomas were found in 83% of cases which is sufficient for diagnostic confirmation. Such result lead us to propose, in patients with suspicious peritoneal tuberculosis, percutaneous liver biopsy as an alternative in first time to laparoscopy which is more invasive.

CONCLUSION

We have found a frequent liver involvement in the case of peritoneal tuberculosis (46%). Cholesterol level lower than 1,31 gr/l was an independent predictor of granulomatous hepatitis in patients with peritoneal tuberculosis. We suggest in this case that percutaneous liver biopsy can be considered as an alternative to laparoscopy.

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