Hypoxic hepatitis : a difficult diagnosis when the cardiomyopathy remains unrecognized and the course of liver enzymes follows an atypical pattern. A report of two cases

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Abstract

In a clinical setting of cardiac or circulatory failure, the diagnosis of hypoxic (ischaemic) hepatitis is easy and can be elicited on mere clinical and biochemical features. We report two cases of hypoxic hepatitis where cardiomyopathy remained unrecognized at admission due to the lack of conventional signs of congestive heart failure and where the increase in liver enzymes activities followed an atypical pattern, characterized by only moderate elevation of serum aminotransferases activities, low ASAT/ALAT ratio and elevated ALAT/LDH ratio. This atypical pattern not suggestive of hypoxic hepatitis, could be explained by a delay between the onset of hypoxic injury of the liver and admission to hospital. Moreover one case was complicated by frank jaundice, an unusual feature in hypoxic hepatitis. Consequently, diagnosis and appropriate inotropic treatment were delayed resulting in progressive deterioration and eventually death of both patients. The report of these two cases and the review of other similar cases previously published, enlighten some atypical features of hypoxic hepatitis. (Acta gastroenterol. belg., **1998**, 61, **385-389**).

Key words : cardiomyopathy, congestive heart failure, diagnosis, hypoxic hepatitis, ischaemic hepatitis.

Introduction

Hypoxic hepatitis (HH) more often called ischaemic hepatitis is well defined by clinical, biochemical and histopathological features. This entity generally occurs in a setting of circulatory failure and the most exposed are patients with decompensated congestive heart failure (1-4). The biochemical hallmark is a dramatic but transient increase in serum lactic dehydrogenase and aminotransferases activities (5). The histopathological examination of the liver typically shows a centrilobular liver cell necrosis with signs of passive congestion (6). Most cases are observed in intensive and coronary care units (3,7). Usually, the cardiac and circulatory features are obvious, making the diagnosis of HH easy. Therefore, it is agreed that an histological confirmation is not mandatory and even inadvisable when 3 conditions are met : an appropriate clinical setting, a sharp increase in serum aminotransferases activities and the exclusion of other causes (viral or drug-induced) of liver cell necrosis (2-4).

Rarely, the diagnosis may be obscured when cardiac failure is not evident whilst clinical features of liver injury are predominant. We report two cases of HH where unrecognized cardiac failure and only moderate increase in serum aminotransferases activities were two pitfalls leading to erroneous diagnosis, delayed appropriate treatment and eventually death of the patients.

Case reports

Case 1

On September 1991, A 77-year-old man was admitted to the emergency room for abdominal pain, bloating and nausea. He was living in an old people's home and was well until 8 days before entry when he complained of abdominal pain, intense fatigue and anorexia. His mental status deteriorated and he became unable to walk alone. His past medical history was dominated by ischaemic cardiomyopathy without infarction but requiring cardiac pacing, 10 years before. His current treatment consisted in isosorbide dinitrate, digoxin, lisinopril, furosemide, buflomedil chlorydrate, haloperidol and lorazepam, all taken for several months. At admission, he was confused but not critically ill. No family contacts could be established and information about his health status remained scarce. Blood pressure was 130/80 mmHg, heart rate 72/min. He was eupneic and could lie flat without respiratory difficulty. Cardiac and pulmonary exams were normal. Discreet ankle edema was noted and mild hepatomegaly (liver span of 12,5 cm in the mid clavicular line) without neck veins distension or hepatojugular reflux. Mental confusion was attributed to cerebrosclerosis but asterixis was present. Blood laboratory data showed : Bilirubin 1.22 mg/dl, ASAT 359 U/L. ($N < 40$), ALAT 384 U/L ($N < 40$), LDH 457 U/L ($N < 200$), CPK 104 U/L ($N < 225$), AP 126 U/L ($N < 115$), GGT 84 U/L ($N < 50$), prothrombin time 41%, Albumin 3.9 gr/dl, Creatinine 2 mg/dl, NH_4 44 meq/L (N 11-35). Blood gaz analysis performed on day 2, showed : PH 7.44, $PaCO_2$ 32 mmHg, PaO_2 72 mmHg, SaO_2 95%. Chest x-ray showed the presence of a pace maker and cardiomegaly without vascular hilar enlargement. Liver ultrasonography performed on admission was reported as normal but actually showed dilatation of inferior

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vena cava and hepatic veins. He was transferred to the Gastroenterology Unit with suspected drug-induced hepatitis secondary to lisinopril. Lisinopril was stopped and during the next eight days, serum aminotransferases activities decreased (fig. 1), while bilirubin, creatinine and prothrombin time improved. Anti HA IgM, HBs Ag, Anti HBC IgM, anti HCV, anti Herpes IgM, anti EBV IgM and anti CMV IgM were negative. On the 8th day, increase in serum transaminases activities recurred (fig. 1) and on day 10, a jugular vein catheter was inserted in order to measure central venous pressure and to perfuse 3 fresh frozen plasma units just before transcutaneous liver biopsy. Central venous pressure raised from 10 cm H_2O to 25 cm H_2O after plasma transfusion. The same day, inotropic intravenous treatment (Dobutamine 10 mg kg^{-1}) was started. The next few days were marked by gradual deterioration of the mental and respiratory status, increase in serum bilirubin to 4.7 mg/dl and serum creatinine to 2.1 mg/dl with fall in prothrombin to 39%. The patient died on day 13. The liver histology showed centrilobular liver cell necrosis and marked signs of passive congestion (dilated sinusoids, hepatocytes atrophy) without inflammatory cells (fig. 2).

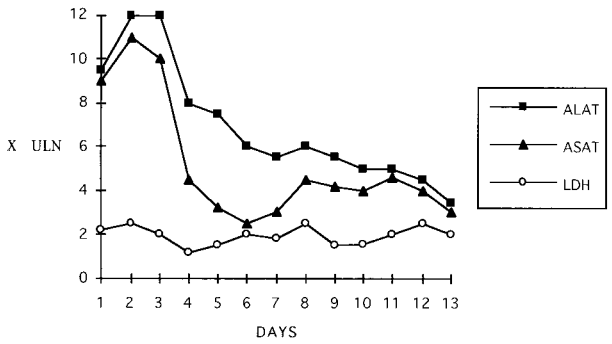


Fig. 1. — Course of serum aminotransferases and lactic dehydrogenase activities in case 1.

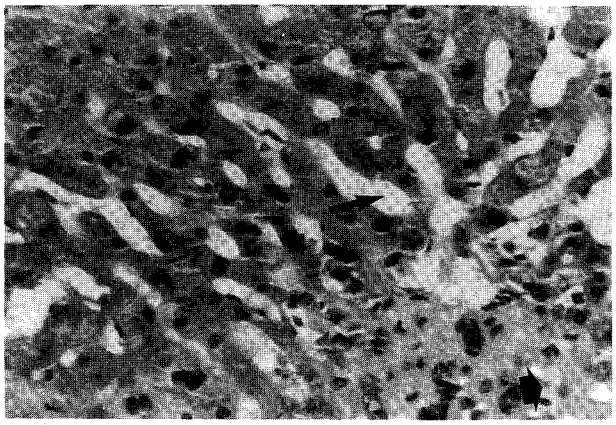


Fig. 2. — Case 1, liver histology, HE, high magnification : centrilobular liver cells necrosis (large arrow) and sinusoidal dilatation (thin arrow).

Case 2

On February 1997, a 63-year-old woman was admitted to the emergency room for jaundice, dehydratation and profound weakness lasting for 4-5 days. She had not experienced fever or abdominal pain. Her past medical history included non insulin dependent diabetes and mild arterial hypertension. She was currently treated by glybenclamide 5 mg/d, metformin 850 mg tid and prazosin chlorydrate 5 mg/d which was stopped 10 days before, following a bout of tiredness and drowsiness. At entry, the clinical examination showed a morbid obese woman with frank jaundice but otherwise in good general condition. Blood pressure was 140/80 mm/Hg, heart rate 80/min and temperature 36.8°C. Cardiac and pulmonary examination were unremarkable. She was eupneic and no ankle edema was present. Abdominal palpation was painless and intestinal sounds were normal. The liver edge could not be appreciated and presence of a hepato jugular reflux was not noted. Main blood laboratory tests were as follows : Bilirubin 14.6 mg/dl, ASAT 142 U/L (N < 40), ALAT 331 U/L (N < 40), LDH 400 U/L (N < 200), CPK 105 U/L (N < 215), AP 115 U/L (N < 115), GGT 78 U/L (N < 50), INR 2.26 corresponding to a prothrombin time of 39%, Albumin 3.5 g/dl, Creatinine 1.9 mg/dl, NH_4 24 meq/L (N 11-35), Fibrin 73 mg/dl, D. Dimers 4.1 µg/ml (N < 0.5), glycemia 232 mg/dl. Electrocardiogram was normal. Chest x-ray and abdomen x-rays were interpreted as normal. Abdominal ultrasonography was difficult to perform due to obesity and showed hyperechogenic liver and gallstones. Intrahepatic bile ducts were not dilated. Nothing peculiar was noted about portal or hepatic veins.

The patient was transferred to the gastroenterology unit with a diagnosis of decompensated diabetes and unexplained hepatitis or possible stone of the common bile duct. Fluid perfusion of 2.5 L/day was ordered. Nothing special was noted the day after. Serology tests for ongoing hepatitis due to HAV, HBV, HCV, Herpes, EBV, CMV were negative as well as auto-antibodies (ANA, SMA, AMA). On day 3, her clinical condition deteriorated, she became sommolent and blood laboratory showed progressive worsening of renal, liver and coagulation tests : creatinine 2.4 mg/dl, Bilirubin 18 mg/dl, INR 2.37, NH_4 50 meq /L (N 11-35), Fibrin 57 mg/dl, D. Dimers 4.4 µg/ml. The evolution of serum aminotransferases activities is reported in fig. 3. She was tranferred to the ICU. At this time, cardiac and pulmonary examination were unmodified and reported as normal. Systolic blood pressure was 109 mmHg and heart rate 77/min. Arterial blood gaz analysis under nasal O_2 2L/min, showed : PH 7.31, $PaCO_2$ 31.6 mmHg, PaO_2 89 mmHg, SaO_2 96%.

Pulmonary artery catheterism (Swan Ganz) was performed and disclosed : central venous pressure 22 cm H_2O (N < 10), systolic pulmonary artery pressure 79 mmHg (N 15-30), mean pulmonary artery pressure 49

mmHg (N 9-16), pulmonary capillary wedge pressure 27 mmHg (N 3-15), cardiac index 1.4 l/min (N 2.8-4.2).

Chest x-ray showed cardiomegaly and pulmonary edema. Cardiac US showed a dilated and hypokinetic left ventricule. Left ejection fraction was estimated between 30-35% (N > 55%). Liver ultrasonography was unmodified. Portal and hepatic veins were reported as permeable.

The condition of the patient rapidly deteriorated despite mechanical ventilation and massive inotropic drugs infusion (Dopamine, Dobutamine, Noradrenalin), unable to sustain a normal arterial pressure. On day 5, blood ammonia rose to 181 meq/L and 2 blood cultures yielded E. coli. She died on day 6, from untractable cardiogenic shock. Autopsy showed moderatly dilated cardiomyopathy with adherent clots in the right atrial and ventricular cavities and past myocardic infarct. The lungs were characterized by pulmonary edema and numerous pulmonary infarcts, with thrombi inside arteries of small and medium size. The liver was congestive and at section had a typical "nutmeg" appearance. Liver histology showed extensive and confluent centrilobular liver cell necrosis. The remaining hepatocytes were reduced to a thin layer around portal spaces (fig. 4).

Discussion

These two cases of hypoxic hepatitis shared some singularities when compared to the usual presentation of hypoxic hepatitis. Both were admitted to the emergency room and lacked usual clinical signs of congestive heart failure like hypotension, tachycardia, dyspnea, orthopnea, cardiopulmonary auscultation signs, jugular veins distension, frank ankle edema. Therefore, a primary liver lesion was suspected and both were transferred to the Gastroenterology Unit rather than to the Intensive or coronary care units. Appropriate treatment was delayed resulting in progressive deterioration and death. Nevertheless, the diagnosis of hypoxic hepatitis is generally easy. In ten years, from 1983 to 1993, we prospectively collected 142 cases of hypoxic hepatitis in the Intensive and Coronary care Units of our hospital. Parts of this series have been previously published (3,7). In most of these cases, the clinical diagnosis was evident on the basis of association of cardiac or circulatory failure and sharp increase in serum aminotransferases activities. The two cases reported herein, escaped the right diagnosis with dramatic consequences. Actually, these two cases illustrate two diagnosis pitfalls and even a third one in the second case : 1) unrecognized cardiomyopathy at entry ; 2) only moderate increase in serum aminotransferases activities and 3) frank jaundice.

The first pitfall was the difficulty to recognize congestive cardiomyopathy at entry. To our knowledge, 4 reports (8-11) including 8 cases have specifically addressed this particular aspect of hypoxic hepatitis.

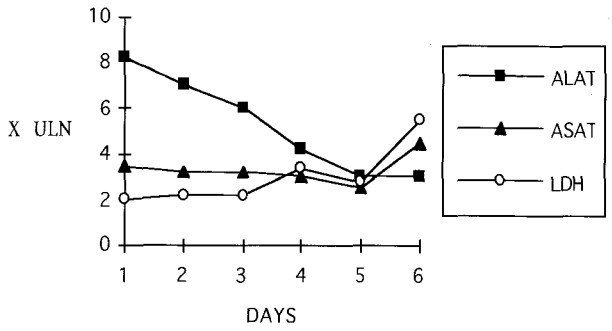
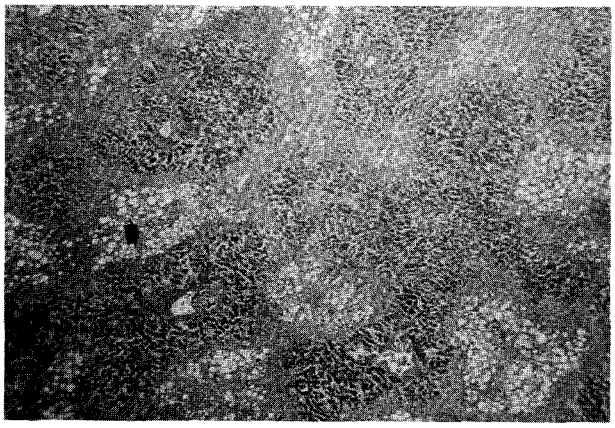


Fig. 3. — Course of serum aminotransferases and lactic dehydrogenase activities in case 2.



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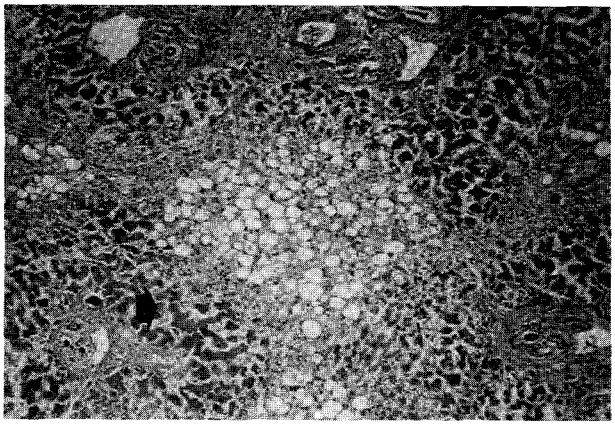

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Fig. 4. — Case 2, liver histology, HE — A)low magnification : extensive and confluent centrilobular liver cells necrosis (arrow) ; B) higher magnification : thin layer of hepatocytes around portal spaces (arrow).

The eight patients, all men, had congestive cardiomyopathy unrecognized as the cause of liver injury due to the lack of conventional clinical signs of heart failure. In three (9,10), the cardiac disease was totally ignored from the past medical history as it was for one of the patients of this report (case 2). In the five others

patients, a clear history of cardiac failure could be elicited, but was asymptomatic at entry and in one case (11) ignored owing to lack of information because of patient mutism and absence of family contacts similarly to the first case of this report. The only clinical signs of cardiac failure in both cases of this report were fatigue and profound weakness as reported in 4 of the 8 cases of the literature (8,9,10). It is noteworthy that in our two patients, some degree of water depletion could be present at admission concealing clinical signs of congestive heart failure : The first patient was taking furosemide and measurement of central venous pressure on day 10 was normal (10 cm H_2O) reaching rapidly the high level of 25 cm H_2O after transfusion of 3 units of fresh frozen plasma ; the second patient was considered as dehydrated at admission secondary to decompensated diabetes and fluid perfusion was ordered. Three of the 4 patients reported by Cohen *et al.* (8), had normal peripheral venous pressure or right atrial pressure and at least 2 of them were taking diuretics.

Abdominal signs like anorexia, nausea, pain in the right upper quadrant were present in one of our cases (case 1) as in at least 5 of the 8 reported cases (8-11). For both patients of this report and the 8 reported in the literature, a primary liver disease, most often viral hepatitis was first suspected. Therefore, these patients were oriented to Gastroenterology, Liver or in one case Psychiatric units (11) and the appropriate treatment was delayed. In 6 cases of the literature, the accurate diagnosis was reached by liver biopsy followed by cardiac evaluation (8,9) and in two cases by cardiac catheterism (10,11) followed by liver biopsy. Both our patients died as did 3 of the 8 patients of the literature.

The second pitfall, an atypical pattern of increase in liver cytolytic enzymes activities (ASAT, ALAT, LDH), has not been previously emphasized. The diagnosis of HH can be reached on mere clinical and biochemical bases (2-4) but it implies strict criteria (12). In typical HH, the rise in serum aminotransferases activities is generally marked, exceeding 20 times the upper limit of normal (ULN) (1-5) and we suggested to not accept the diagnosis of HH in the absence of histological confirmation if the rise remains less than 20 $\times$ ULN (12). Moreover, the rise in serum LDH is also particularly impressive and Cassidy *et al.* have shown that a ratio of ALT/LDH (expressed in $\times$ ULN) less than 1.5 can differentiate hypoxic (ischemic) hepatitis from viral hepatitis (13). Finally the course of enzymes activities is also typical : the LDH peak is early and very transient (5). The ASAT peak generally precedes the ALAT peak and is higher. The decrease in ASAT activities, however is more rapid due to shorter half life and after 2-3 days, enzymes activities curves tend to cross. The normalization or near normalization of serum aminotransferases activities occurs in $\sim$ 7 days (1-5). No part of this typical pattern was observed in both patients of the present report : The maximum increase in serum ASAT and ALAT activities reached 11 ULN and 12 ULN in case 1 and 3.5 ULN and 8.2 ULN in case 2 respectively. The ALAT/LDH ratio never fell under 1.5 in case 1 and reached this low value only on the 4th day in case 2 (fig. 1 et 3). In both patients, the serum activities of ALAT were higher than that of ASAT and the slopes of regression of enzymes activities were unusually slow or fluctuant (fig. 1 and 3). This quite atypical pattern could be explained first, by a delay in admission to the hospital and second by a delay in the administration of the appropriate treatment. An admission delay between the onset of the liver hypoxic injury and the entry to hospital could explain the moderate rise in serum enzymes activities, the higher level of ALAT activities and the atypical ALAT/LDH ratio for hypoxic hepatitis. The first patient of this report was complaining of extreme fatigue and weakness for a week and the second had experienced an episode of fatigue and drowsiness ten days before entry. The delay in administration of the appropriate treatment could result in a prolonged hypoxic injury of the liver explaining the slow and even fluctuant (case 1) regression of serum enzymes activities. A slow and fluctuant regression of enzyme activities was also observed in 5 of the 8 similar cases reported in the literature (8-11).

Frank jaundice is a third diagnosis pitfall as illustrated by the second case of this report. Frank jaundice is unusual in HH. In our prospective series of 142 cases of HH (partly published in 3, 7), serum bilirubin exceeded 10 mg/dl in only 5 patients, three of then having another underlying liver disease, cirrhosis in 2 and extensive metastatic infiltration in one. We are aware of only two case reports addressing this unusual aspect of HH (14,15). In both cases, HH resulted from cardiac failure with a protracted course and poor therapeutic response. Nevertheless, a relationship between the rise in serum bilirubin and the extension of centrilobular liver cell necrosis has been recognized since the precursory study of Sherlock in 1951 (16).

Finally, the two cases of this report make clear the controversy about the frequency of HH. Investigators potentially interested in the field of HH are mainly gastroenterologists or hepatologists, but HH unless if atypical is rarely observed in Internal Medicine Units. Birgens *et al.* collected 5 cases from the Internal Medicine Units of several Copenhagen hospitals during a 12 year-period (17) while Bynum *et al.* collected 7 cases in the internal service of the John Hopkin's hospital during a 5 year-period (1). On the other hand, by investigating charts of patients hospitalised with extreme elevation of serum ASAT activity, Hickman *et al.* collected 29 cases of HH during a 6 month-period in an Australian hospital (18) and Johnson *et al.*, 32 cases during a one-year-period in a tertiary American hospital (19). Ourselves, we prospectively collected 142 cases of HH during a 10-year-period in a single general hospital, while we just observed these 2 atypical cases during a 5-year-period in the Gastroenterology Unit.

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