Hemorrhagic cholecystitis as a likely cause of nontraumatic hemobilia in metachromatic leukodystrophy: report of a case

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Abstract

A 17-years-old man with the juvenile form of MLD developed massive hemobilia. CT and US scans showed blood and clots filling the gallbladder and the biliary ways, with no bleeding source seen at selective angiography. Explorative laparotomy evidenced bleeding from a papillomatous gallbladder mucosa, resolved with cholecystectomy. Histologic examination with specific colorations diagnosed hemorrhagic cholecystitis from metachromatic leukodystrophy of the gallbladder. This is, to our knowing, the third case reported in Literature, and thus hemorrhagic cholecystitis may be considered a life-threatening complication of MLD to be prevented with cholecystectomy as soon as signs of gallbladder pathology (papillomatosis/polyposis, jaundice, abdominal pain) are suspected.
Key words: Hemorrhagic cholecystitis, hemobilia, metachromatic leukodystrophy.

Riassunto

LA COLECISTITE EMORRAGICA COME CAUSA DI EMOBILIA NON TRAUMATICA NELLA LEUCODISTROFIA METACROMATICA: CASO CLINICO

Un paziente di sesso maschile di 17 anni affetto da una forma giovanile di leucodistrofia metacromatica ha sviluppato una massiva emobilia. La Tomografia Computerizzata e l'Ecografia hanno evidenziato la colecisti e le vie biliari ripiene di sangue e coaguli, senza che l'angiografia selettiva abbia potuto evidenziare l'origine del sanguinamento. La laparotomia esplorativa ha evidenziato l'origine del sanguinamento nella mucosa papillomatosa della colecisti e quindi il paziente è stato sottoposto a colecistectomia. L'esame istologico ha consentito di porre diagnosi di colecistite emorragica da leucodistrofia metacromatica della colecisti. Si tratterebbe, per quanto è dato sapere, del terzo caso riportato in letteratura e pertanto la colecistite emorragica può essere considerata una minacciosa complicanza della leucodistrofia metacromatica, può essere prevenuta attraverso una tempestiva colecistectomia al primo sospetto di patologie a carico della colecisti (papillomatosi/poliposi, ittero, dolori addominali).
Parole chiave: Colecistite emorragica, emobilia, leucodistrofia metacromatica.

Introduction

Metachromatic leukodystrophy (MLD) is a neurologic disease, transmitted in a recessive autosomic way; the enzymatic deficiency is attributed to arylsulfatase A (mapped in cr. 22) or to SAP-1 (sphingolipid activator protein mapped in cr. 10). It is characterized by a progressive demyelination of the white matter due to abnormal sulfatide storage in brain, peripheral nerves, and in extraneuronal sites such as liver, distal nephronic tubules, spleen, lymph nodes, testis, bone marrow and gallbladder (1). About the latter site, several reports have underlined the importance of gallbladder polyposis in MLD (2, 3, 4), but, to our knowing, only 2 other cases have been described in Literature as presenting a massive upper gastrointestinal bleeding (5, 6), as occured to our patient.

Case history

A 17-years-old male was transferred from a medical ward for the oncoming of hematemesis and maelena in a patient affected by the juvenile form of MLD in study for jaundice, pyrexia and abdominal pain. He soon worsened to hypovolemic shock, treated with fluid resuscitation and blood transfusions. Hemoglobin value was 5.2 g/dl, with a hematocrit of 15%, 18800 WBC/μl, total

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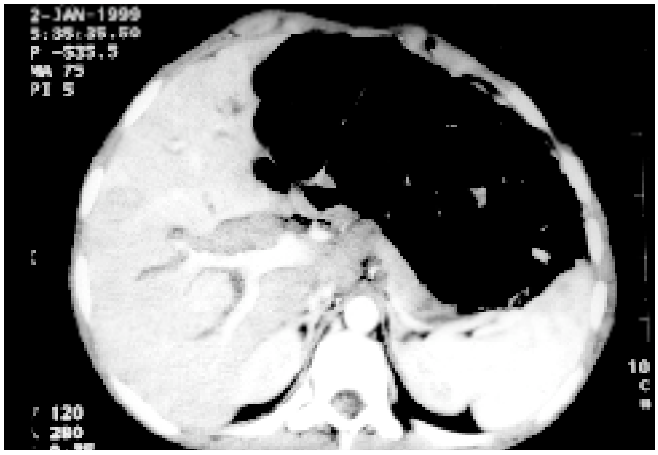

Fig. 1: Abdomen angio-CT scan showing dilatation of the intrahepatic bile ducts filled with dishomogeneous material.

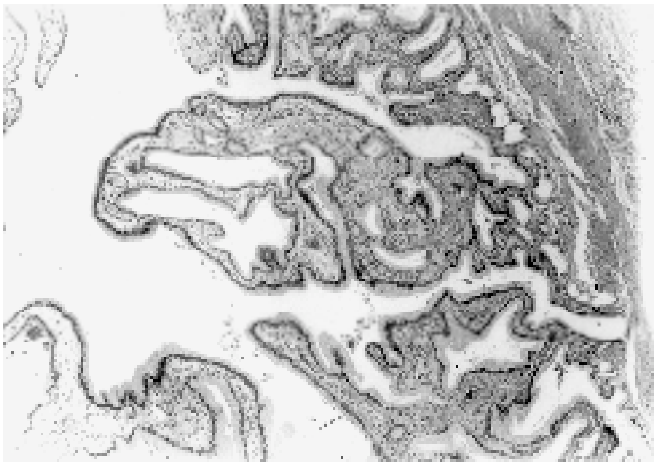

Fig. 2: Hematoxylin and eosin stain (4 x): Gallbladder mucosa shows pseudopolyps with dilated glands bulging into the lumen: they are characterized by numerous hystiocytes, rare inflammatory elements and a preserved epithelium.

bilirubin of 8.73 mg/dl and elevated values of cholestasis (dir. bil. = 7.28 mg/dl, SGOT = 323 U/l, SGPT = 723 U/l, ALP = 454 U/l, GGT = 232 U/l). Esophagogastroduodenoscopy (EGDS) and endoscopic retrograde colangiography and pancreatography (ERCP) showed a blood clot covering the papilla Vateri, that gave start to active bleeding at removal. Computed tomography (CT) of upper abdomen evidenced a dilatation of the gallbladder, of the intra and extrahepatic bile ducts and of the initial tract of the duct of Wirsung, filled of a dishomogeneous material suspected of being fresh blood mixed with clots (Fig. 1). Selective angiography exluded the presence of vascular abnormalities without evidence of any source of active bleeding. Despite 6 units of blood transfusal, hemoglobin values kept lowering, and so the patient underwent explorative laparotomy: after isolation of hilar hepatic structures, transversal choledocotomy was performed; fiber-optic choledoscopy evidenced blood clots extending upwards to the cystic duct, with dilatation of the proximal biliary tree that showed no bleeding sources. Incision of the gallbladder permitted the removal of a voluminous intraluminal clot, covering an irregular mucosa of pseudopolypoid appearance, actively bleeding, resembling a sub-mucosal angioma. A cholecistectomy was performed and was followed by the disappearance of any bleeding at the choledocoscopic control.The closure of the choledocotomy, protected by the insertion of a t-tube concluded the operation. Microscopic examination evidenced a hyperplastic mucosa (without atipies or displastic cells), raised to form multiple pseudopolypoid formations, a thick gallbladder wall with oedema, hemorrhagies, capillary congestion and microthrombosis extended to the peri-visceral tissue, together with an inflammatory infiltrate, and excluded the presence of any vascular malformation, configuring a diagnosis of acute necrotizing cholecystitis (Fig. 2). However the foamy aspect of histiocytes suggested an enzime deficiency accumulation disease in absence of familiar hypercholesterolemia or hemolitic crises, and the scarcity of inflammatory elements without abscesses and atrophy of the mucosal layer did not justify such an important pathological outcome. These elements induced us to look for the presence of sulfatides, in order to determine an etiology connected with his neurologic disease: in fact the presence of metachromatic sphingoglicolipid material evidenced by histologic colorations with Toluidine blue (Fig. 3), Cresyl violet and PAS (with and without digestion) strongly suggested the diagnosis of metachromatic leukodystrophy of the gallbladder.
The post-operative recovery was uneventful, cholestasis and hemoglobin parameters normalized, and the t tube was removed after a normal cholangiogram. The patient is still alive after one year without complications.

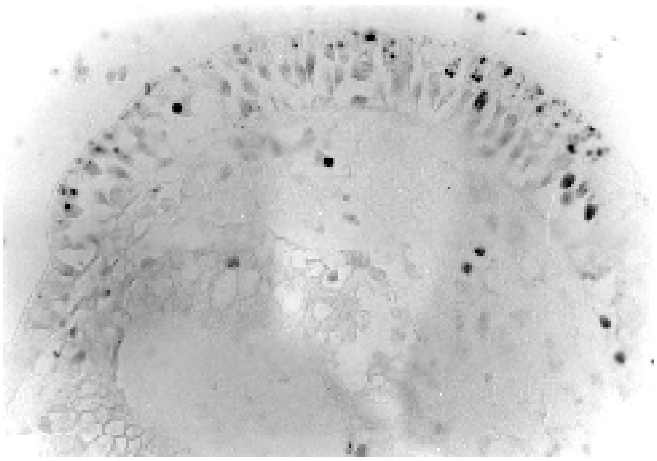

Fig. 3: Toluidine blue stain (40 x): Superficial epithelium contains numerous metachromatic granules at Toluidine Blue; the same material is evident in fibroblasts and in stromal endothelium.

Discussion

Biliary tract haemorrhage is one of the less frequent causes of upper gastrointestinal bleeding (7). The term hemobilia was at first defined by Sandblom in 1948 for a case of traumatic genesis (8). It can be caused by lesions due to trauma, lithiasis, vascular abnormalities, inflammation, neoplasms or parasitic infections to liver, gallbladder, biliary ducts or pancreas (9). While in the past the most frequent affections were of traumatic origin, recent studies have ascribed to interventional radiology the greatest part in causing minor hemobilia, due to the significant increase in invasive procedures (hepatic biopsies, percutaneous transhepatic cholangiography, trans-hepatic alchoolizations etc) (10). Hemobilia of cholecistic origin accounts for about 23% of the cases in literature (11), and the clinical presentation with overt G.I. hemorrhage is extremely rare, being prevalentely due to lithiasis or to necrotizing gangrene of the gallbladder wall (12, 13). The typical clinical presentation of massive hemobilia has been synthetized by Quinke in 1871 (abdominal pain, jaundice and gastrointestinal hemorrhage); the obstruction of bile ducts by blood clots and their consequent dilatation justifies jaundice and the typical colicky pain. In the frequent impairment of superior cerebral functions typical of MLD symptoms are often hard to distinguish, and may be misleading. To our knowing only two cases of hemobilia related to MLD have been described in Literature: the former, by Cappel et al. (6) regarded a 37 years old man affected by the adult form of MLD, complaining of right upper quadrant abdominal pain, jaundice, melena and pyrexia which underwent, as in our case EGDS, ERCP, abdomen-US, angiography and intraoperative choledoscopy before making the diagnosis of massive hemobilia (that required five units of blood transfusal) from a gallbladder polyp (3.0 x 0.4 cm) in a contest of gallbladder polyposis, treated with cholecystectomy. The latter case, described by Siegel et al. (5) , also concerned a 27 years old man with an adult type of MLD which developed, instead, repeated epysodes of upper GI bleeding (four times, noone causing a lowering of hemoglobin values under 9.0 g/dl) due to hemobilia, in which the final diagnosis was made with a gallbladder biopsy in course of ERCP, demonstrating metachromatic material in its wall, in a contest of papillomatosis of the mucosa as seen after cholecistectomy.

In both cases papillary or polypoid lesions were found at macroscopic and microscopic examination, and the histological characteristics were similar (hypertrophied mucosa, thickened wall, inflammation, intramuscular and subserosal hemorrhages): in the former, though, no specific colorations were made to search for sulfatides, using only hematoxylin and eosin stains.

The latter case has been studied more completely, with Toluidine blue stains and also with lipid stainings (not feasible in our specimen for it was formalinized).

In our case, the first described in the juvenile form of MLD, gallbladder mucosa appeared interested by important hyperplasia with pseudopolypoid aspect, erosions and necrotic areas, in which we also found abnormal storage of glicolipidic metachromatic material at Toluidine, PAS, PAS-D and Cresyl violet stains.

Esophagogastroduodenoscopy is often the first line exam in the suspect of hemobilia, permitting to diagnose the absence of more frequent causes of upper gastrointestinal bleeding, like peptic ulcers or esophageal varices, and can sometimes evidence a clot covering the papilla Vateri.

The role of ultrasounds and angio-CT has been stressed by some Authors (14, 15) and, although their utility is limited to distinguishing indirect signs of bleeding, they can be expecially useful in hemorragic cholecystitis; in fact these exams can detect the presence of blood in the lumen of gallbladder and biliary ducts, but are unable to describe the precise site of bleeding. In the cases described by Cappel and by Siegel the US-scan had led to the diagnosis of mucosal lesions ascribed to polyposis/papillomatosis of the gallbladder wall: instead, in our case, the gallbladder was contracted, and thus the exam resulted non-diagnostic, being it necessary to perform a CT scan (not performed in the two previously described cases), more sensible in determining the hemorrhagic nature of the liquid that filled the biliary ways, but less sensible on gallbladder wall lesions.

On the other hand, angiography, gold standard exam in hemobilia of vascular and traumatic origin, for his proved diagnostic and therapeutic effectiveness, is, like in our case and in the former two cases, frequently non-diagnostic in gallbladder bleedings, which are typically not persistent and/or inferior to 1 ml/min (16), and has proven to be negative even when massive bleeding (documented by active oozing from the papilla in our case) is in act.

ERCP, when feasible (depending on the entity of duodenal bleeding through the papilla), permits a good definition of biliary tree lesions (traumatic, neoplastic, obstructive) and Siegel reports the utility of making a gallbladder biopsy during the procedure for the diagnosis of sulfatide storage in MLD (5).

Anyway, like happened in the case described, the evaluation of the nature and site of biliary bleeding is often demanded to surgical exploration, and eventually to intra-operative choledoscopy.

In our case the suspect of a bleeding from the gallbladder has derived from the absence of blood in the biliary tree proximal to the origin of the cystic duct, and was confirmed by the demonstration of active bleeding from the inner gallbladder wall, but most of all by the sudden stop of biliary bleeding after removal of the gallbladder.

Cholecystectomy is the procedure of choice in these cases, and the insertion of a t tube is recommended, to protect the biliary suture, and expecially to have an easy post-operative way to control the main biliary duct.

Conclusions

We think that this case, for his particularity, can underline the opportunity to suspect a gallbladder involvement in those rare cases of MLD patients complaining of upper right quadrant abdominal pain, that may be caused by mechanical obstruction of the cystic duct, either by polyps or clots from minor bleeding, so that a correct diagnosis is obtained and eventually cholecistectomy performed before the onset of massive bleeding, which can occur lately, and precipitate the patient to a life-threatening condition. Moreover, considering that pathological involvement of the gallbladder by abnormal sulfatide storage can precede the oncoming of neurological symptoms and consequently the diagnosis of MLD (expecially of the adult type), we suggest to look for the presence of metachromatic material in the histological specimen (bioptic or operatory) with "ad hoc" colorations (including those for lipids, like Sudan Black, that can be diagnostic only on fresh material) and electron microscopy, in all those cases of gallbladder polyposis or hemorrhagic cholecystitis of unclear etiology expecially in children and young adults.

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