# Jaundice in a pregnant woman

Sophiane Ibrahimi, Abbas Ali Mroué, Erik Francois, Robert Jagodzinski

Service de Gastro-entérologie, CHU Tivoli (ULB), La Louvière, Belgium.

## Abstract

**A 34-year-old woman in the 22nd week of gestation presented with generalized pruritis and weight loss since the first trimester of pregnancy. Physical examination revealed cutaneous scratch lesions, jaundice, and hepatomegaly. Blood tests revealed cholestasis with elevated direct bilirubinemia. Auto-antibody and viral hepatitis tests were negative. Liver ultrasound was normal. The initial diagnosis was cholestasis of pregnancy. However despite treatment with ursodeoxycholic acid, the patient did not improve. Delivery was by cesarean section at the 26th week of pregnancy for obstetrical reasons. A new liver ultrasound showed a heterogeneous nodular mass. Nuclear magnetic resonance (NMR) of the liver showed an 11-cm mass centered on the hilum, dilated intrahepatic bile ducts, involvement of the hepatic veins, and hilar adenopathy. A liver biopsy revealed fibrolamellar hepatocellular carcinoma (FHC).** (Acta gastroenterol. belg., **2017**, 80, **422-424**).

**Key words :** pregnancy and Fibrolamellar.

## Introduction

A 34-year-old woman in the 22nd week of gestation presented with generalized pruritis and weight loss since the first trimester of pregnancy. Physical examination revealed cutaneous scratch lesions, jaundice, and hepatomegaly. Blood tests revealed cholestasis with elevated direct bilirubinemia. Auto-antibody and viral hepatitis tests were negative. Liver ultrasound was normal. The initial diagnosis was cholestasis of pregnancy. However despite treatment with ursodeoxycholic acid, the patient did not improve. Cesarean section was performed at the 26th week of pregnancy for obstetrical reasons. A new liver ultrasound showed a heterogeneous nodular mass. Nuclear magnetic resonance (NMR) of the liver showed an 11-cm mass centered on the hilum, dilated intrahepatic bile ducts, involvement of the hepatic veins, and hilar adenopathies. A biopsy of the mass revealed fibrolamellar hepatocellular carcinoma (FHC). FHC is a rare tumor, representing less than 1% of malignant primitive liver tumors. Affected patients are typically young, of either sex, without pre-existing liver disease. Alpha-foetoprotein levels are normal, and the diagnosis may be suggested by NMR imaging. Treatment consists in surgical resection. Prognosis is better than for common hepatocellular carcinoma. Recurrence is frequent and rapid. There is no known effective adjuvant therapy.

## Case report

A 34-year-old woman in the 22nd week of gestation presented with generalized pruritis and subjective (undocumented) weight loss since the first trimester of pregnancy. She had no significant past medical history and took no medication. During the second trimester of pregnancy, she presented with cholestatic symptoms (jaundice, pale stools, and dark urine). There was no history of vomiting. Physical examination revealed cutaneous scratch lesions, jaundice, and mild hepatomegaly. Blood tests upon admission to the emergency room showed elevated leucocytes at 15590/mm3 and C-reactive protein at 2 mg/dl (upper limit of normal range, ULN: 1.2 mg/dl). Liver tests showed AST at 47 U (ULN: 37 U), ALT at 56 U (ULN: 41), GGT at 118 U (ULN: 55 U), Alkaline Phosphatase at 1754 U (ULN: 129 U) and a total bilirubin at 4.22 mg/dl (ULN: 1.2 mg/dl), with direct bilirubinemia at 3.98 mg/dl (ULN: 0.6 mg/dl).

The patient was admitted for observation. A liver ultrasound with Doppler imaging was normal. An auto-immune workup was negative (antinuclear, anti-smooth muscle, anti-liver-kidney microsome, anti-soluble liver antigen, anti-liver cytosol type 1 and anti-mitochondrial type M2 antibodies). Total immunoglobulin levels were normal. There were no signs of iron deficiency. Viral serologies were negative (hepatitis A, B and C; herpes simplex virus; cytomegalovirus; Epstein Barr virus; and human immunodeficiency virus).

Considering a negative liver workup, the diagnosis of intrahepatic cholestasis of pregnancy was suggested and ursodeoxycholic acid, 250 mg tid, was initiated. Of note, no dosage of bile salts was performed.

At week 26 of pregnancy, the patient presented with increased fatigue and jaundice had worsened despite treatment. Delivery was performed by caesarean section for obstetrical reasons. Laboratory tests showed increased total and direct bilirubin (respectively 7.61 and 6.99 mg/dl).

A liver ultrasound was obtained, revealing a large heterogeneous nodular mass. NMR imaging showed an 11-cm liver mass, heterogeneous, with irregular borders, centered on the hilum, with dilated intrahepatic bile ducts. Contrast injections showed arterial-phase uptake of the lesion. Tumor markers alpha-foetoprotein,

Correspondence to : Abbas Ali Mroué, CHU Tivoli, Department Gastro-enterologie, 7100 La Louvière.
E-mail : Abbasmroue@yahoo.fr

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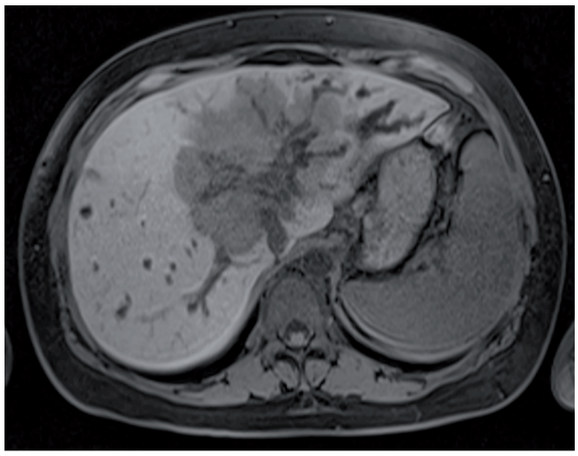

Figure 1.A. — NMR T1-weighted sequence, no iv contrast. Solid focal mass spanning both liver lobes and hilum.

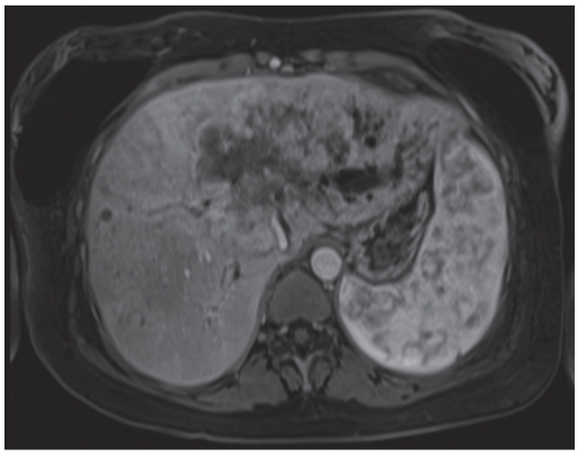

Figure 1.B. — T1-weighted sequence, hepatic phase with iv contrast showing heterogeneous uptake.

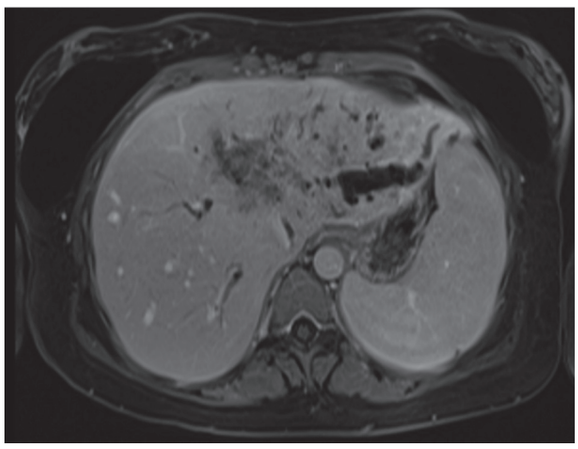

Figure 1.C. — T1-weighted sequence in portal phase showing homogeneous uptake.

carcinoembryonic antigen, and CA-19-9 were normal. The hepatic tumor was unresectable due to involvement of the hepatic veins. There were multiple enlarged lymph nodes at the liver hilum (Fig. 1). A CT-guided biopsy was performed. Histology showed tumoral proliferation of hepatocytes with anarchic internal structures. The

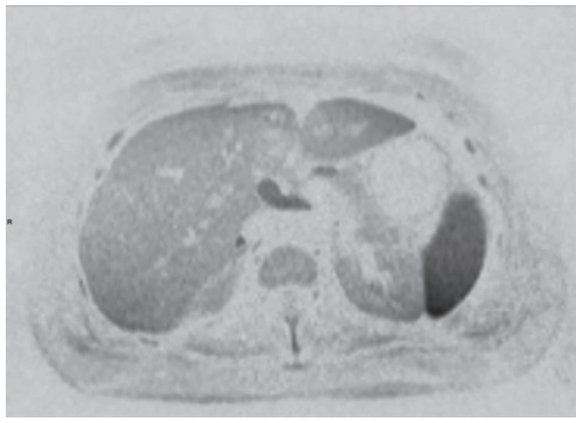

Figure 1.D. — Diffusion study. Visualisation of liver hilum adenopathies.

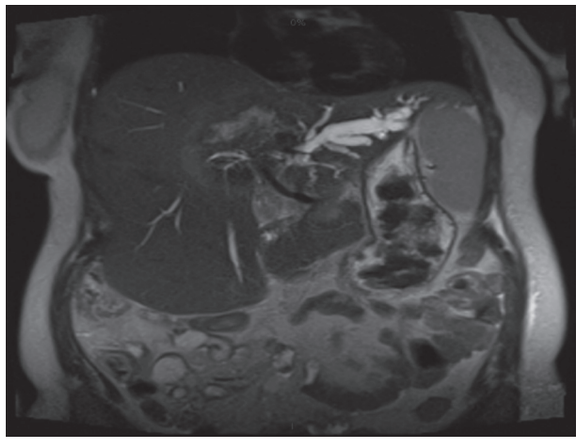

Figure 1.E. — NMR T2-weighted sequence shows dilated bile ducts.

hepatocytes, some enlarged and polygonal, presented abundant granular cytoplasm and sac-shaped nuclei (Fig. 2). There was a low nuclear to cytoplasmic ratio. There were laminated fibrous layers of collagen interspersed between the hepatocytes (Fig. 3). These images were suggestive of fibrolamellar hepatocarcinoma. A positron emission tomography (PET)-CT scan showed a hypermetabolic uptake in the lymph nodes of the hepatic hilum. Endoscopic ultrasound-guided fine needle aspiration of these nodes was performed : cytology showed no malignant cells.

The patient was referred for liver transplantation and benefitted from a living-donor liver transplant. Evolution at 6 months was favorable. Histology of the explant showed a 10.5 cm mass, with extensive necrosis, and confirmation of the diagnosis of FHC. All resected lymph nodes (n = 6) were free of malignancy.

## Discussion

FHC is a rare disease, described by Edmondson in 1956. It is considered a variation of typical hepatocellular carcinoma, with very different clinical and epidemiological characteristics. It occurs most often in

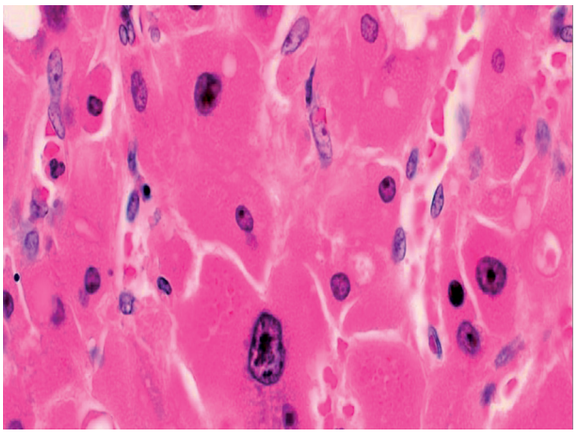

Figure 2. — Tumoral hepatocytes are large, polygonal, and with abundant cytoplasm.

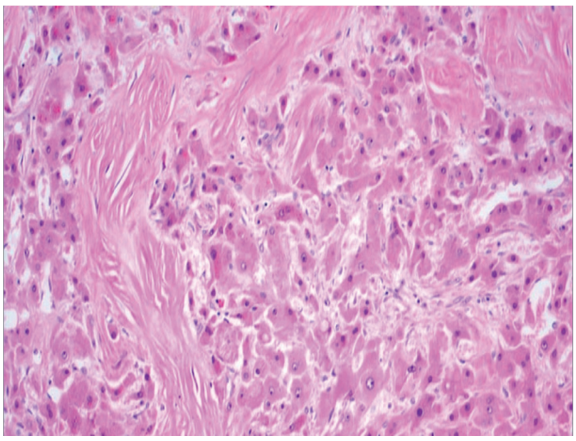

Figure 3. — Hepatocytes separated by laminated layers of fibrous collagen.

relatively young (65% are diagnosed before the age of 40), in Caucasians, with no gender preference and no underlying liver disease. FHC has no known risk factor. It represents less than 1% of primary liver malignancies. Incidence is estimated at 0.02 cases per 100000 (1). Symptoms are not specific and include abdominal pain and weight loss. Jaundice may be present. Hepatomegaly is frequent. Alpha fetoprotein is usually normal. Serum decarboxyprothrombin has been shown to be elevated in FHC, as has neurotensine. There may be decreased levels of vitamin B12 binding protein (2-4). Upon diagnosis, the tumor is often large (greater than 5 cm in 65% of cases), perhaps because of slow growth. It is most often solitary. NMR is the most effective diagnostic tool. The lesion is often a will-defined tumor (80-100% of cases), with signal intensity decreased in T1-weighted sequences, and increased in T2-weighted sequences. Arterial sequences show heterogeneous contrast uptake, while portal sequences show homogeneous uptake. A central fibrous scar is present in 70% of cases with, typically, decreased signal intensity in T1 and T2-weighted sequences, which differentiates it from the fibrous scar in focal nodular hyperplasia (where signal intensity is increased in T2 images) (2). CT may also show the central scar, as well as calcifications (68% of cases) (2). Histologically, the diagnosis of FHC depends on the presence of large malignant cells, often polygonal in shape, with abundant eosinophilic cytoplasm and a large nucleus. The malignant hepatocytes are separated by dense laminated fibrous layers of collagen. Immunohistochemical testing show that tumoral cells express cytokeratin 7 but not alpha-foetoprotein (2). Frequent sites of metastasis include lymph nodes (60% of cases), lung, and peritoneum (3). The treatment of FHC consists in partial hepatectomy with lymphadenectomy (46-55% of cases) (4-5) or liver transplantation (23% of cases) (4). There is no other systemic or loco-regional treatment known to be effective (6).

In their detailed review, Eggert et al. report that overall prognosis is better for FHC than for typical hepatocellular carcinoma, with a 5-year survival rate of 33.6% vs 16.1%. However, only 20% of hepatocellular carcinoma subjects were in the "radiofrequency ablation or resection or transplant" treatment group versus 46% of FHC subjects, with survival rates of respectively 51.1% and 56.8%. The authors note that FHC may not be less aggressive than typical hepatocellular carcinoma. Rather, FHC may have an overall better prognosis because it occurs in younger subjects with previously healthy livers and a high proportion of resectable tumors (5). Recurrence is frequent (36-100% in different case series) and precocious (1-3 years) (6).

## Conclusion

In summary, FHC, while rare, makes up a significant proportion of hepatocellular carcinomas occurring in young people. It has a better prognosis than typical hepatocellular carcinoma, especially after complete resection, but carries a high recurrence rate. After surgical treatment of recurrence, 5-year survival is 28%. There is no effective adjuvant therapy available.

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