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Total hepatectomy and liver transplant for hepatocellular adenomatosis and focal nodular hyperplasia*

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Abstract. Extensive hepatocellular adenomatosis (HA) and focal nodular hyperplasia (FNH) represent a proliferation of hepatic cells that occurs most frequently in women. These lesions are uncommon in the pediatric age group, accounting for 2 % of pediatric hepatic tumors, and are extremely rare in males. The etiology of HA and FNH has been correlated with the use of oral contraceptives. We report to the best of our knowledge the first series of patients treated with OLTx for HA and FNH (five cases). All these patients had lesions involving at least 90 % of the hepatic parenchyma and all underwent major hepatic surgery before OLTx because of life threatening complications. One patient died in the immediate postoperative period following retransplantation for primary non-function of the first OLTx. Four out of five patients are currently alive from 4.1 to 9.6 years after OLTx. Our results justify the use of OLTx for symptomatic patients with HA and FNH who cannot be treated with conventional hepatic resections.

Key words: Hepatocellular adenomatosis – Focal nodular hyperplasia – Liver transplantation

Indications for orthotopic liver transplantation (OLTx) have been continuously expanding. Hepatic replacement for primary and metastatic malignancy of the liver has been the subject of numerous reports [7, 14, 17, 18, 21, 23, 30]. Nevertheless, the indication for such aggressive therapy for benign neoplasms of the liver has yet to be defined. The role of OLTx for extensive hepatic adenomatosis (HA) and focal nodular hyperplasia (FNH) is analyzed in this study.

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HA is a disease seen mainly in women. Before the use of oral contraceptives, HA was amongst the rarest of tumors. In two large pathological reviews of material collected between 1907 and 1954, only six patients with HA were found [2, 9]. Since the use of oral contraceptives from 1960, more examples of liver cell adenomas have been published [1]. It is also possible to observe lesions of this type even in the pediatric age group [29]. The term FNH was introduced in 1958 by Edmondson [4]. It occurs most often in women and can be associated with oral contraceptives [16]. This pathological process has also been described as occurring in pediatric patients [27].

Because of the characteristics of these two liver lesions, treatment of symptomatic patients usually consists of surgical resection. In fact the majority of these tumors may be resected with conventional subtotal hepatectomies.

This study describes our experience in patients treated with OLTx for multiple HA, with one patient having associated extensive FNH. In all five patients, more than 90 % of the liver parenchyma was involved with the lesions, thus preventing a curative hepatic resection.

This report represents, to the best of our knowledge, the first series of OLTx for multiple HA and for FNH with long-term follow-up.

Case reports

Case 1

Patient 1, a white female born in 1965, was referred for OLTx evaluation in January 1982 because of end-stage liver disease secondary to type I glycogen storage disease and HA. She had undergone an end-to-side portacaval shunt 9 years previously to improve her growth and the metabolic abnormalities associated with glycogen storage disease [8, 24].

During this period the child was followed with serial sonographic examinations of the liver which began to reveal intrahepatic masses. Until 1981, no symptoms were referable to these masses. However, a liver biopsy of one lesion was obtained and this proved to be an adenoma.

In September 1981 the patient had the onset of severe abdominal pain and tenderness with enlargement of her liver. This was thought

to be due to intrahepatic hemorrhage resulting in obstruction of the biliary tree and subsequent hepatic failure. The patient's condition deteriorated further 3 months later. Abdominal CT scan confirmed that hepatomegaly was secondary to multiple intrahepatic masses (Fig. 1). She was placed on the transplant list due to progressive liver failure, the potential risk of malignant transformation of the HA, and because the lesions appeared to be unresectable by a conventional approach. At OLTx her native liver was found to be enlarged with the parenchyma almost completely replaced by multiple nodules, which histologically proved to be adenomas (Fig. 2).

The patient developed portal vein thrombosis 1 year after OLTx with hepatopetal collateral circulation adequately perfusing the liver. Because of repeated episodes of gastrointestinal tract bleeding, she underwent a distal spleno-renal shunt for control of portal hypertension [19]. Over the past 9 years, her liver function has been excellent, and the most recent liver enzyme levels performed in August 1991 were normal.

Case 2

Patient 2, a white female born in 1948, presented in November 1980 with abdominal tightness, anorexia and weight loss. An abdominal CT scan demonstrated multiple defects within the liver. There was no history of birth-control pill ingestion, although in May 1980 she presented with menorrhagia which was successfully treated for an 11-day period with hormone replacement.

In December 1980, because of dyspnea secondary to ascites and liver enlargement, a laparotomy was performed. She was found to have multiple masses in both lobes of the liver, and a large amount of hemorrhagic ascites. Liver biopsy was consistent with multiple HA. The patient was referred to our institution for further evaluation. A right hepatic trisegmentectomy was performed. The remaining portion of the left lobe still had some residual nodules. The histologic diagnosis on the removed parenchyma was multiple HA with no evidence of malignancy. Tamoxifen was started in an attempt to prevent further growth of the residual adenomas.

In January 1982 the patient presented with increasing abdominal girth and a palpable abdominal mass. Abdominal CT scan demonstrated massive enlargement of the residual lateral left segment due to multiple large masses, which occupied most of the parenchyma. The patient was activated as a liver transplant candidate, and a suitable donor became available on 5 March 1982. At surgery the residual left lobe of the liver was markedly enlarged. The hepatectomy specimen weighed 4250 g. Histological examination demonstrated multiple HA replacing almost the entire liver parenchyma, with signs of focal necrosis and cholestasis. The postoperative course was uneventful and she was discharged.

In August 1991 she was found to have multiple lesions in the lungs. These lesions proved to be metastases possibly of hepatocellular carcinoma. However, pathology failed to reveal any malignant lesion in the native liver at the time of OLTx, and no lesions were found at CT scan of the transplanted liver in August 1991. The most recent liver function tests performed in August, 1991, more than 9 years following OLTx, were normal.

Case 3

Patient 3, a black female born in 1965, had a history of oral contraceptive use since age 13 years. She presented with moderate pruritus and hepatomegaly 2 years later. A diagnosis of possible multiple HA was entertained, based on ultrasound and CT examinations showing multiple low density lesions involving both lobes of the liver. In May 1981, she had an episode of intraabdominal hemorrhage (from one of the adenomas) requiring emergency operation and left lateral segmentectomy. Examination of the surgical specimen confirmed the diagnosis of HA. Subsequently the patient has several episodes of intrahepatic bleeding which led to the resection of a segment of the right lobe 18 months later. In March 1983 the patient was referred to our institution for possible OLTx. Abdominal CT showed recurrence of the lesions with involvement of the entire liver (Fig. 3). The patient was felt to be a suitable candidate for OLTx. An OLTx was performed on 25 September 1984. The native liver weighed 2600 g with distortion of the parenchyma by numerous soft lobulations. Histologic examination confirmed the diagnosis of multiple HA.

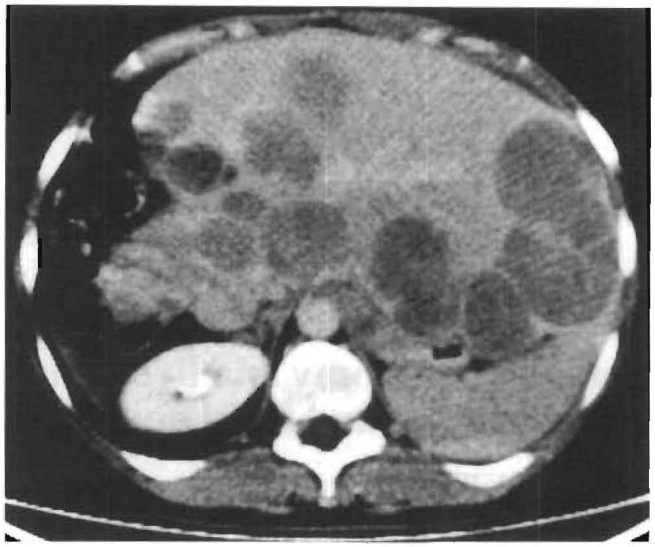

Fig. 1. Pre OLTx CT scan, case no. 1. Multiple hepatic masses occupying almost all the liver parenchyma

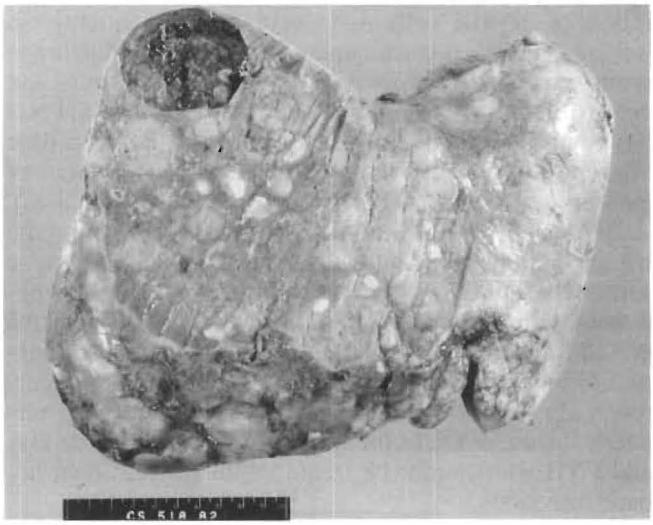

Fig. 2. Case no. 1, recipient liver (a portion has been removed for biochemical study). Multiple nodules distorting the surface are clearly discernible

The patient's quality of life in the last seven years has been excellent. She graduated from college Nursing School and is working full time. The most recent liver function tests performed in September 1991 were normal.

Case 4

Patient 4, a white female born in 1977, had a familial history of liver adenomatosis. Her mother underwent a liver resection for HA in 1981 and presently was four new HA. Her 8-year-old brother also has multiple HA. Since age 7 years the patient has had multiple recurrent episodes of abdominal pain. In May 1987 an ultrasound and CT scan of the liver revealed the presence of multiple masses, the

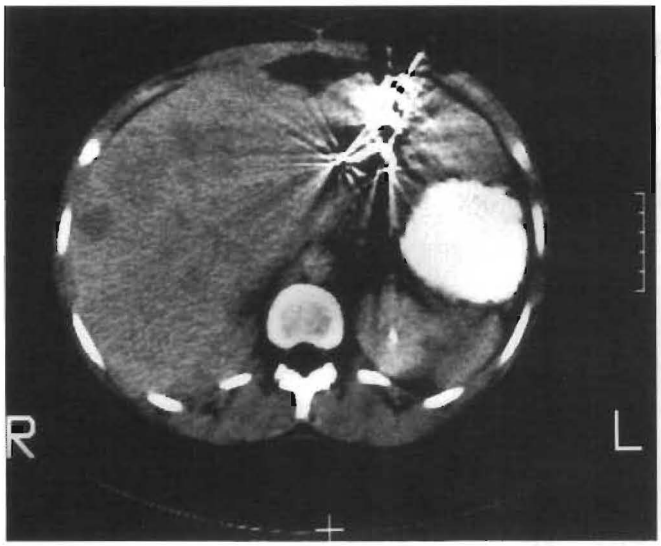

Fig. 3. Pre OLTx CT scan, case no. 3. Surgical clips (related to previous left and right segmental resection) can be noted in the liver. Inhomogenicity with multiple low density areas can be noted throughout all lobes of the liver

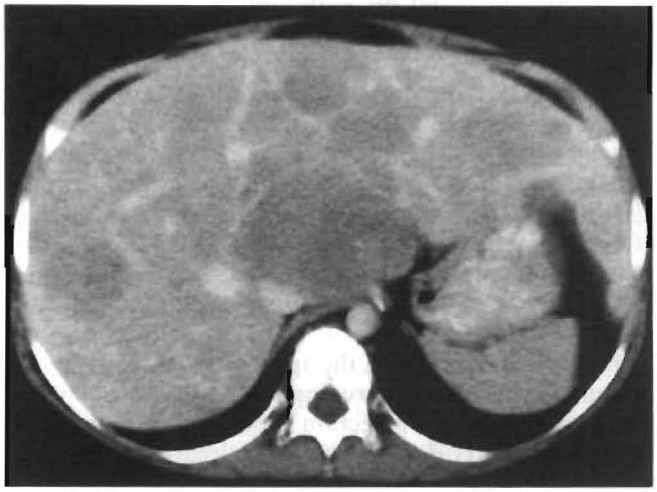

Fig. 4. Pre OLTx CT scan, case no. 4. Multiple hepatic mass lesions of various sizes are spread throughout the entire liver

largest of these being 10 cm in diameter (Fig. 4). In June 1987 she developed fever and abdominal pain. Repeat ultrasound and CT scan of the abdomen revealed a mass with an air fluid level in the right lobe of the liver consistent with an abscess. The remaining hepatic parenchyma was replaced by tumor. At laparotomy the abscess including a portion of the tumor and normal appearing liver were excised for histology. Material was also sent for cultures. Histology confirmed the presence of a HA with associated hemorrhage and necrosis; cultures were positive for Salmonella. The pathological characteristics of the patient's tumor resembled those of her mother.

She was referred to our institution 2 months later for transplant evaluation. Abdominal CT showed inhomogeneity with multiple low-density areas throughout all lobes of the liver (Fig. 4). She was found to be a good candidate of OLTx because of her progressive clinical deterioration and the unresectability of her lesions. The hepatectomy specimen showed multiple tumor masses measuring from 0.5 to 7.0 cm in diameter and replacing 90% of the liver parenchyma (Fig. 5). In addition to adenomas, histology revealed multiple lesions of FNH.

She is presently in excellent condition, attending school full time, and the last liver function tests performed in August 1991 were normal.

Case 5

Patient 5, a white female born in 1944, had a long history of diarrhea which had been ascribed to irritable colon syndrome. In April 1987 an abdominal CT scan showed multiple masses in the liver. She then underwent a laparoscopy with liver biopsy and a diagnosis of adenoma was made. The patient had been taking daily 17-alfa-estradiol therapy for 2 years up until she was discovered to have hepatic ademonas.

In October 1987 she presented to another institution with acute onset of dull right upper abdominal quadrant pain. A new CT scan performed at that time revealed two small areas suspected of blood collections inside of the right lobe of the liver. The patient was transferred in stable condition to our institution for further evaluation. The other parameters were unremarkable. CT scan of the abdomen showed hepatic adenomas involving the entire left lobe with extension into the anterior segment of the right lobe (Fig. 6). She was considered to be probably not treatable with conventional hepatic resection and she was activated as a liver transplant candidate with the idea to attempt a left trisegmentectomy when a liver became available. A suitable donor was identified on 24 December 1987, and the patient was explored. The liver seemed almost completely replaced by multiple adenomas, except for the anterior segment of the right lobe which appeared free of disease. A left trisegmentectomy was attempted. However, residual adenomas were encountered in the intersegmental plane between the anterior and the posterior segments of the right lobe. Consequently, a decision was taken to perform an OLTx. The patient required 129 units of packed red blood cells during the procedure, and this was probably partially related to her high presensitization and the presence of cytotoxic antibodies (PRA 50%) [20]. Histological examination of the native liver showed multiple HA replacing almost the entire liver parenchyma with both small and large cell dysplasia of a mild to moderate degree, but no definite evidence of malignancy. The transplanted liver underwent primary non-function and the patient developed renal failure. On 27 December 1987, she underwent a second OLTx. The second liver functioned, but she developed severe necrotizing pancreatitis and died on 4 January 1988.

Discussion

Hepatic adenomas and FNH represent a proliferation of hepatic cells that occurs most frequently in women [5]. These lesions are very rare in the pediatric age group accounting for 2% of hepatic tumors [3], and extremely rare in males [5]. A strong relationship has been postulated between HA and the use of oral contraceptives [1, 5, 15]. Even FNH may be hormone dependent [15], and is often associated with use of birth-control pills [5, 16]. Hepatic adenomas have also been reported as a frequent complication of metabolic diseases, including type I glycogen storage disease, galactosemia, and tyrosinemia [5, 10].

These aspects of HA and FNH are represented in the patients of our series of whom all were female. Two of them were in the pediatric age. One had used oral contraceptives for several years. One had received short-term hormone therapy for menhorragia, while another had 2 years of estrogen administration before the clinical onset of the liver disease. The background for the multiple HA in one patient was type I glycogen storage disease.

Both HA and FNH are benign tumors but their definitive diagnosis can only be made on the basis of the micro-

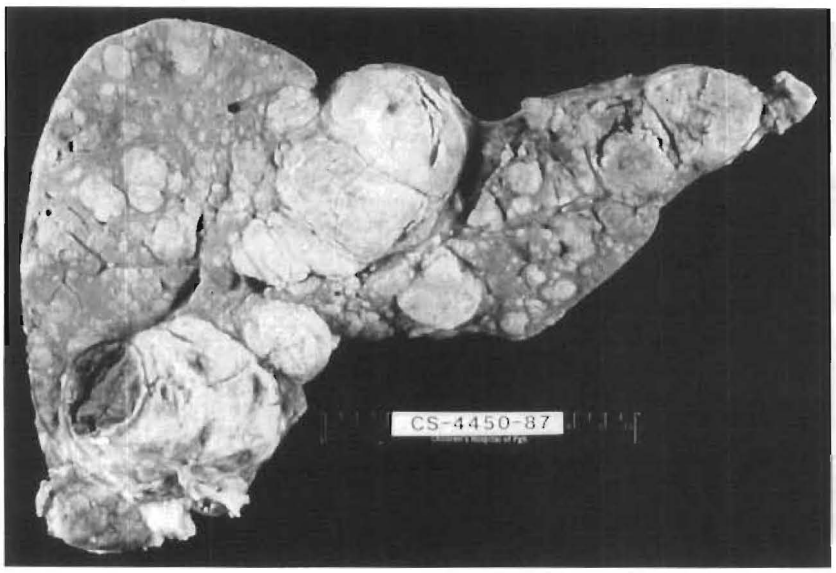

Fig. 5. Case no. 4. Cross-section of the recipient liver. The parenchyma is in most part replaced by circumscribed, irregular nodules ranging from 0.2 to 7.0 cm

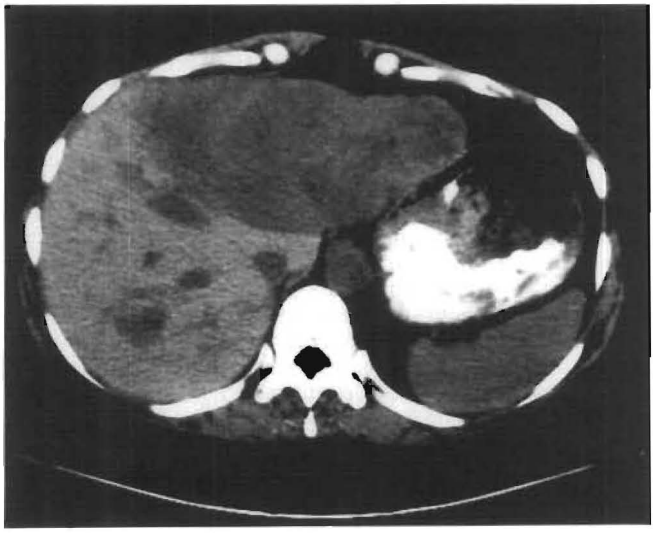

Fig. 6. Pre OLTx CT scan, case no. 5. A large hypodense lesion is demonstrated involving the entire left hepatic lobe with extension into the anterior segment of the right lobe. There is an additional smaller round lesion in the posterior segment of the right lobe

scopic examination of the biopsy material. Radiological examinations including ultrasound, radionuclide scintigraphy, CT and angiography are helpful in studying, grading and following the patient, but they cannot offer absolute diagnostic parameters. The histological differential diagnosis for HA includes hepatocellular carcinoma and hepatoblastoma in the pediatric population [11, 28]. HA can be differentiated from FNH because the former does not contain bile ductules, which are always present in FNH [4].

The clinical history in our patients suggested relatively fast-growing hepatic lesions. The median interval from the first diagnosis to OLTx was 20 months (range: 7 months to 4 years).

The usual clinical presentation of HA is different from that of FNH. Generally adenomas result in bleeding and necrosis, as occurred in all four of our HA cases. Emergency surgery is required for intraabdominal hemorrhage in one third of the patients [5], and this had been the case in patients no. 2 and no. 3. In contrast FNH is usually asymptomatic and commonly is an incidental clinical or autopsy diagnosis [5, 15]. In patient no. 4 who had mixed HA and FNH, symptoms were from a liver abscess.

The development of hepatocellular carcinoma within a HA have been reported in a few patients taking oral contraceptives [15] and in patients with type I glycogen storage disease [31]. Reports have described regression of HA after discontinuation of birth control pills [6, 26] and of cases of regression with dietary therapy in patients whose HA was associated with type I glycogen storage disease [22].

Both for HA and FNH, the approach to therapy should be conservative. If there are single or few lesions, exploratory laparotomy and resection should be recommended for HA and FNH if conventional extirpation techniques are feasible. In extensive cases of asymptomatic FNH, a biopsy to confirm the diagnosis and a long-term radiological non-invasive follow-up may be preferable to a dangerous extensive resection. Even large lesions may be stable for a lifetime. However, the diagnosis must be certain, and it must be recognized that in expert hands, even hepatic trisegmentectomies can be done safely [12–14, 25].

Watching and waiting is a less attractive option for HA because the natural history is unpredictable and the possible risks of bleeding and malignant transformation are higher. In our patient no. 2, lung metastases of hepatocellular carcinoma were found 9.5 years after OLTx without evidence of tumor recurrence in here native liver which was removed in two stages separated by more than a year, or in the transplanted liver.

In the cases reported here, drastic treatment was indicated. The lesions which occupied 80% or more of the liver, were symptomatic, multiple and non-resectable short of fatal hepatectomy. The 80% long-term survival (mean 7.5 years) provides retrospective justification as well as encouragement for further trials in similar highly selected patients.

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