Hepatic Pseudotumor in Long-Standing Biliary Atresia Patients Undergoing Liver Transplantation

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A pseudotumor, giant regenerative nodule, or macroregenerative nodule is an unusual benign hepatic lesion in biliary atresia (BA) patients. This tumor may mimic malignant transformation and may preclude liver transplantation (LT). The clinical and imaging surveillance of patients after the Kasai procedure is therefore an important aspect of management of BA patients. Our objective is to report our experience and describe the incidence, imaging, and pathologic features of pseudotumors in BA patients awaiting LT. From August 1990 to December 2006, 133 LTs for BA were performed. Five (3.8%; 4 female, 1 male) patients were diagnosed with pseudotumor. The patients' records were reviewed. The diagnostic imaging modalities used were abdominal ultrasound (US), computed tomography (CT) scan, and magnetic resonance imaging (MRI). Histologic confirmation of the lesions was obtained in all cases. All underwent the Kasai operation in early infancy. Six of 7 lesions in 4 of 5 patients were demonstrated by pretransplant imaging. Two of 7 tumors were detected by US. Five of 7 lesions were detected by CT, and 5 of 7 lesions were demonstrated by MRI. In 1 patient, the lesion was not seen in the US, CT, or MRI but was found during surgery and confirmed by histology. An additional tumor was found incidentally during histologic examination in a patient previously diagnosed to have 2 tumors by CT and MRI. In another patient diagnosed to have 2 tumors on imaging, pathology revealed only a single tumor. In conclusion, although unusual, pseudotumor should be included in the differential diagnosis of liver masses in BA children. Liver Transpl 13:1545-1551, 2007. © 2007 AASLD.

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Biliary atresia (BA) is the most common cause of chronic cholestasis in infants and children.1-5 This obstructive cholangiopathy leads to early development of secondary biliary cirrhosis.2,3 The Kasai hepatopancreatoenterostomy has improved the outcome of BA patients, particularly if performed on children <90 days old,6 but is usually not curative as liver function continues to deteriorate because of recurrent cholangitis and cirrhosis. As many as 67% of these patients will develop chronic liver disease, and almost all will require liver transplantation (LT) before reaching adulthood. Continuing cholangitis promotes biliary fibrosis and portal hypertension. These eventually lead to cirrhosis and predispose to malignant change.

BA is the most common indication for pediatric LT, representing at least 50% of all pediatric cases.7 We have published our clinical experience with 100 living donor liver transplantations (LDLTs) for BA.8 Further analysis of this series showed that a pseudotumor (giant regenerative nodule or macroregenerative nodule)
mimicking malignant transformation occurred in rare instances that may have precluded LT. The clinical and radiologic surveillance of patients after the Kasai procedure is therefore an important aspect of management of patients with BA. A pseudotumor is a benign lesion that usually presents as an asymptomatic liver mass and must be distinguished from other benign or malignant hepatic lesions. We have encountered patients with hepatic pseudotumors on routine evaluation for LT for end-stage liver disease patients secondary to BA. The incidence, diagnostic imaging appearances, pathologic findings, and clinical importance of this type of tumor are discussed.

PATIENTS AND METHODS

From August 1990 to December 2006, 133 pediatric LTs for BA (110 living donor, 23 deceased donor) were performed at the Chang Gung Memorial Hospital Kaohsiung Medical Center (Taiwan). The records of these patients and their follow-up were retrospectively analyzed; this included recipient demographic data, preoperative imaging, preoperative alpha-fetoprotein (AFP), operative outcome, type of graft, pathology of the explanted liver, complications, and long-term outcome. Particular attention was given to patients whose preoperative imaging showed hepatic tumors.

Diagnostic Imaging

Routine pretransplant imaging modalities included liver ultrasound (US) with Doppler scans, triphasic contrast computed tomography (CT) scan and computed tomography angiography (CTA), and magnetic resonance imaging (MRI). The CT of the liver with and without contrast enhancement and with CTA was done from the lower chest to upper abdomen in a 1-mm contiguous section with reconstruction of 5 mm. The contrast agent was given via mechanical intravenous injection at 2.5-3 mL/second. Scanning was under the control of subtraction that included the arterial, portal, and venous phases. Reconstruction of the vascular images was performed according to the pathway of the hepatic artery, portal vein, hepatic vein, and inferior vena cava.

MRI of the liver with and without contrast enhancement and with magnetic resonance angiography was performed under pulse sequences as follows: axial-gradient T1-weighted images, T2-weighted images, and long timed-echo T2-weighted images with an 8-mm thickness and 2-mm gap. Axial-gradient T1-weighted images with contrast were taken 15 seconds after intravenous infusion of gadopentetate dimeglumine (gadolinium, 0.2 mL/kg body weight) with an 8-mm thickness and 2-mm gap. This was followed by 30-second intervals for the second and third T1-weighted images with contrast. Magnetic resonance angiography with reconstruction of vascular images was also performed according to the pathway of the hepatic artery, portal vein, hepatic vein, and inferior vena cava.

All patients underwent routine imaging except the first patient (LDLT 60), who did not undergo MRI. This patient was a foreigner and had complete pretransplant workup prior to referral. An algorithm for the pretransplant evaluation process for transplant candidates is presented in Fig. 1.

**TABLE 1. Demographic and Clinical Profile of Biliary Atresia Patients with Pseudotumor**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (months)</th>
<th>Gender</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Child’s PELD Months After Kasai</th>
<th>Presentation</th>
<th>AFP</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDLT 60</td>
<td>31</td>
<td>Male</td>
<td>90.5</td>
<td>15.0</td>
<td>7 3</td>
<td>Liver mass</td>
<td>&lt;0.3</td>
</tr>
<tr>
<td>LDLT 178</td>
<td>121</td>
<td>Female</td>
<td>141.8</td>
<td>34.6</td>
<td>10 1</td>
<td>Liver mass</td>
<td>&lt;0.3</td>
</tr>
<tr>
<td>LDLT 192</td>
<td>36</td>
<td>Female</td>
<td>96.0</td>
<td>17.0</td>
<td>7 2</td>
<td>Liver mass</td>
<td>&lt;0.3</td>
</tr>
<tr>
<td>LDLT 201</td>
<td>228</td>
<td>Female</td>
<td>161.7</td>
<td>50.8</td>
<td>9 10</td>
<td>No liver mass</td>
<td>&lt;0.3</td>
</tr>
<tr>
<td>LDLT 251</td>
<td>204</td>
<td>Female</td>
<td>150.7</td>
<td>54.6</td>
<td>7 10</td>
<td>Liver mass</td>
<td>&lt;0.3</td>
</tr>
</tbody>
</table>

Abbreviations: AFP, alpha-fetoprotein; LDLT, living donor liver transplantation; PELD, Pediatric Model for End-Stage Liver Disease.
Histopathologic Analysis

Histologic confirmation of the lesions was obtained in all cases. The explanted liver was examined by 1 experienced liver transplant histopathologist. All specimens were sliced at 5-mm intervals, and detected tumors were carefully noted and examined. The liver underwent histopathologic and immunohistochemistry studies to determine degree of cirrhosis and hepatitis virus activity, if present. Liver inflammation grading was based on the Hepatitis Activity Index score. If malignancy was noted, malignant tumor grading was performed according to the Edmondson criteria. Lymph nodes were also examined.

RESULTS

Five (3.8%) patients were diagnosed to have hepatic pseudotumors on the basis of combined clinical, imaging, and pathologic findings. There were 4 female and 1 male patients. The mean age was 124 months (range, 31-228). All underwent the Kasai operation in early infancy. In 4 patients, the tumors were diagnosed preoperatively, whereas in 1 patient (LDLT 201), the diagnosis was made during surgery and upon review of the histopathology of the explanted liver specimen. One patient (LDLT 251) was diagnosed to have both hepatocellular carcinoma and hepatic pseudotumor, but pathology showed only a giant regenerative nodule. Only 1 patient (LDLT 60) underwent pretransplant tumor biopsy, which showed no malignant cells. AFP was normal in all patients. The demographic, clinical, and pretransplant profiles of the patients are summarized in Table 1.

All 5 patients underwent LDLT. Two patients received extended left lateral segment grafts. Another 2 teenage patients received right lobe grafts, and 1 patient received a left lobe graft. All patients are surviving with their original grafts. The mean follow-up was 30.8 months (range, 10-61).

Diagnostic Imaging Characteristics

Six of 7 lesions in 4 of 5 patients were demonstrated by imaging. Two of 7 tumors were detected by US. Both were described as hypoechoic lesions. The sonographic studies did not show any particularly significant pattern for the diagnosis of pseudotumor. Moreover, it was more difficult to detect tumors in the background of macronodular cirrhosis.

Five of 7 lesions were detected by CT. Precontrast and postcontrast delayed scans were obtained in all patients. Four lesions were identified on early phase scan as isodense with a vascular bundle inside the tumor and surrounding vascular rim. Septation-like structures were also noted inside the tumor in 3 lesions. The delayed scan showed isodense to hypodense lesions. In 1 lesion (LDLT 60), the early phase scan showed significant enhancement of the tumor that persisted during the delayed phase scan and was suggestive of a hypervascular tumor (Fig. 2). In another lesion (LDLT 251),
the CT revealed a hypervascular tumor with early enhancement during the early phase scan and early washout in the delayed scan suggestive of hepatoma.

Five of 7 lesions were demonstrated by MRI. In 4 lesions, the tumor presented as hyperintense in T1-weighted images and isointense or hypointense in T2-weighted images. A vascular bundle was also noted inside the tumor, and the tumor had a surrounding vascular rim. In 1 lesion, the MRI showed a bright tumor in both T1-weighted and T2-weighted images with early enhancement typical of hepatoma (Fig. 3). One patient did not undergo MRI.

In 1 patient (LDLT 201), the lesion was not seen in the US, CT, or MRI. One lesion was found during surgery and confirmed by histology in this patient. An additional tumor was found incidentally during histologic examination in a patient previously diagnosed to have 2 tumors by CT and MRI (LDLT 192). In another patient (LDLT 251) diagnosed to have 2 tumors on imaging, pathology revealed only a single tumor. Table 2 summarizes the imaging characteristics.

Histopathologic Characteristics

In all specimens, the liver showed marked cirrhotic change, with thick fibrotic bundles containing small proliferating bile ductules and surrounding the regenerative liver cell nodules. The nontumoral liver parenchyma revealed micronodular cirrhotic change with small liver cell nodules surrounded by thick fibrous septa with mild lymphocytic infiltration and numerous bile ductules. Cholestasis and bile plug filling the bile ducts and stromal tissue were also noted. The pseudotumor was composed of benign-looking liver cells arranged in 1- to 2-layer cell plates with intervening sinusoidal spaces and scattered venous structures and abortive portal zones with bile ducts (Fig. 4). This picture was suggestive of a macroregenerative nodule.

All tumors were described as macroregenerative nodules showing marked cirrhosis with variously sized small regenerative liver cell nodules surrounded by broad fibrotic septa. Prominent ductular proliferation and lymphocytic infiltration existed in the fibrotic bands. In 1 specimen, focal dense acute and chronic inflammatory cell infiltration but few ductules were seen in the fibrotic bands. Some mononuclear cell infiltration was also noted.

Immunohistochemical staining in 1 specimen demonstrated the macroregenerative lesion to have partial sinusoid capillarization, as evidenced by CD34 immunostaining. The Ki-67 staining was <1% and showed low proliferative activity. These results were compatible with a regenerative nodule.

Figure 3. LDLT 251. (A) The computed tomography scan showed early enhancement of the tumor. (B) A bright tumor in T1-weighted and T2-weighted images was seen on magnetic resonance imaging scans (indicated by arrows). (C) The explanted liver with tumor.
DISCUSSION

A pseudotumor, giant regenerative nodule, or macroregenerative nodule is an unusual benign hepatic lesion infrequently seen in BA patients. In this series, we defined its incidence to be 3.8%. Grossly, a pseudotumor is a well-circumscribed lesion. Hemorrhage or necrosis may be rare because of good vascularity, as represented by a vascular bundle inside the tumor and the surrounding vascular rim seen on imaging and evidenced by the scattered venous structures seen on histology. These gross findings are typical of focal nodular hyperplasia (FNH) without the central fibrous scar. In FNH, the central scar is surrounded by nodules of hyperplastic hepatocytes along with Kupffer cells and proliferating bile ductules and is composed of invariably vascularized fibrous connective tissue. It has been theorized that a pseudotumor represents an extreme form of architectural distortion in longstanding cirrhosis.

In this review, the US features of a pseudotumor were nonspecific for tumor differentiation. Because a pseudotumor contains normal liver tissue, it can be deduced that this type of tumor will be isodense to low intensity when compared with the liver parenchyma on CT or isointense to low intensity on MRI. The CT demonstrated the characteristic tumor vascularity. The isodense lesion rapidly enhances in the arterial phase of contrast-enhanced CT. This hypervascularity may be transient and visible only in the arterial phase, although persistent hypervascularity may also be seen. If imaged during the portal venous enhancement, the lesion may become isoattenuated with respect to the normal liver tissue and difficult to visualize. This hypervascularity may be attributed to the vascular bundle inside the tumor and vascular rim surrounding the tumor, where feeding tumor vessels arise.

The MRI provided additional information about the characteristics of the lesion. Pseudotumors in this series are hyperintense in T1-weighted images and become hypointense in T2-weighted images. This characterization describes the central scar in FNH and is seen in about one-third of cases. Whether a pseudotumor is a precursor tumor to FNH seen in cirrhotic livers needs further epidemiologic and clinicopathologic analyses.

Because the typical imaging features of a pseudotumor have not been described, its differentiation from other primary and secondary hepatic lesions seen in children is difficult. The lesions most likely to be confused with a pseudotumor aside from FNH are hepatoblastoma, hepatocellular carcinoma, hepatic hemangioendothelioma, liver cell dysplasia, and hepatic adenoma. Hepatic adenomas in children are usually associated with glycogen storage disease and are often multiple. A peripheral tumor capsule thought to be helpful in distinguishing hepatocellular carcinoma can also be seen in a pseudotumor, as demonstrated in this review, where rim enhancement is present in the pseudotumor capsule. Although FNH may show radiologic features similar to those of a pseudotumor, the surrounding liver of a giant regenerative nodule shows cirrhotic features. Benign lesions seen on CT in longstanding BA also include bile duct dilatation and biliary infarction. An elevated AFP level may suggest the presence of a malignant tumor, but further workup is warranted even in the presence of a normal AFP level.

The role of US among compensated BA patients waiting for transplant is mainly in surveillance to detect tumor lesions because it is cheap and readily available. Because it may be difficult to detect tumors in a background of macronodular cirrhosis, CT is an alternate imaging modality. Because of its invasiveness and the potential problem of needle-track seeding if the tumor is proven malignant, CT-guided biopsy of identified tumors in children should be undertaken in cases in which clinical, imaging, and laboratory parameters cannot exclude the possibility of malignancy and the tissue diagnosis affects the overall management (for example, surgical extirpation, transplantation, or adjuvant treatment). It must also be emphasized that having primary malignancy (for example, hepatocellular carcinoma, hepatoblastoma, or hemangioendothelioma) in the liver is not a contraindication for transplantation as long as the tumor is in the liver and it fulfills the accepted set of criteria for transplantation. The algorithm presented here (Fig. 1) is based on our experience with

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**TABLE 2. Imaging Features of Biliary Atresia Patients with Pseudotumor Pretransplant**

<table>
<thead>
<tr>
<th>Case</th>
<th>Number of Tumor</th>
<th>Size (cm)</th>
<th>Ultrasound</th>
<th>CT Enhancement</th>
<th>CT Density</th>
<th>MRI Enhancement</th>
<th>MRI Intensity</th>
</tr>
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<tbody>
<tr>
<td>LDLT 60</td>
<td>1</td>
<td>10</td>
<td>Hypoechoic</td>
<td>(+)</td>
<td>Hypodense</td>
<td>No MRI</td>
<td></td>
</tr>
<tr>
<td>LDLT 178</td>
<td>1</td>
<td>7</td>
<td>Hypoechoic</td>
<td></td>
<td>Isodense</td>
<td>Hypointense T2</td>
<td></td>
</tr>
<tr>
<td>LDLT 192</td>
<td>2</td>
<td>7.2</td>
<td>No mass</td>
<td>No mass</td>
<td></td>
<td>Hypointense T2</td>
<td></td>
</tr>
<tr>
<td>LDLT 201</td>
<td>2</td>
<td>0.6</td>
<td>No mass</td>
<td>(+)</td>
<td></td>
<td>No mass</td>
<td></td>
</tr>
<tr>
<td>LDLT 251</td>
<td>2</td>
<td>3.5, 6</td>
<td>No mass</td>
<td>(+)</td>
<td></td>
<td>Isointense T1, T2</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CT, computed tomography; LDLT, living donor liver transplantation; MRI, magnetic resonance imaging.
the last 2 cases as our pretransplant imaging process in the first 3 cases was evolving at that time and we saw this rare pseudotumor only 3 times in a span of 7 years before the fourth case.

In conclusion, a pseudotumor in BA patients undergoing LT, although unusual, shows a wide spectrum of findings on various imaging modalities. The performance of routine imaging modalities (US, CT, and MRI) should be periodically undertaken to detect tumor lesions, to differentiate benign lesions from malignant lesions, and for follow-up comparison in longstanding BA patients. Pseudotumor should be included in the differential diagnosis of liver masses in children.

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