Benign Liver Masses and Lesions in Children: 53 Cases over 12 Years

Israel N. Kochin MD, Tamir A. Miloh MD, Ronen Arnon MD, Kishore R. Iyer MD, Frederick J. Suchy MD and Nanda Kerkar MD

Pediatric Hepatology, Division of Pediatric Hepatology and RMTI, Department of Surgery, Mount Sinai School of Medicine, New York City, NY, USA

ABSTRACT: Background: Primary liver masses in children may require intervention because of symptoms or concern about malignant transformation.

Objectives: To review the management and outcome of benign liver masses in children.

Methods: We conducted a retrospective chart review of children with liver masses referred to our institution during the period 1997–2009.

Results: Benign liver masses were identified in 53 children. Sixteen of these children (30%) had hemangioma/infantile hepatic hemangioendothelioma (IHH) and 15 (28%) had focal nodular hyperplasia. The remainder had 6 cysts, 4 hamartomas, 3 nodular regenerative hyperplasia, 2 adenomas, 2 vascular malformations, and one each of polyarteritis nodosa, granuloma, hepatic hematoma, lymphangioma, and infarction. Median age at presentation was 6 years, and 30 (57%) were female. Masses were initially noticed on imaging studies performed for unrelated symptoms in 33 children (62%), laboratory abnormalities consistent with liver disease in 11 (21%), and palpable abdominal masses in 9 (17%). Diagnosis was made based on characteristic radiographic findings in 31 (58%), but histopathological examination was required for the remaining 22 (42%). Of the 53 children, 27 (51%) were under observation while 17 (32%) had masses resected. Medications targeting masses were used in 9 (17%) and liver transplantation was performed in 4 (8%). The only death (2%) occurred in a child with multifocal IHH unresponsive to medical management and prior to liver transplant availability.

Conclusions: IHH and focal nodular hyperplasia were the most common lesions. The majority of benign lesions were found incidentally and diagnosed radiologically. Expectant management was sufficient in most children after diagnosis, although surgical intervention including liver transplant was occasionally necessary.

KEY WORDS: hemangioendothelioma, focal nodular hyperplasia

Primary liver masses constitute the third most common group of solid abdominal tumors of childhood [1,2], with an incidence of 0.4 to 1.9 per million children each year [3]. Liver masses in children can be malignant, benign, or indeterminate [4]. Although improved radiographic modalities facilitate the identification of benign and malignant liver masses [2], differentiation of masses is still complex, and biopsy or resection for histological diagnosis sometimes becomes necessary [5-8]. Serum tests of alpha-fetoprotein level may be elevated in children with malignant lesions such as hepatoblastoma (90%) and hepatocellular carcinoma (50%), but cautious interpretation is warranted as alpha-fetoprotein level is frequently elevated in premature and/or normal infants up to 6 months of age and may be slightly elevated with benign tumors and with hepatic insulin or regeneration [5,9].

Benign primary liver masses described in children include hemangioma/infantile hepatic hemangioendothelioma, focal nodular hyperplasia, simple hepatic cysts, mesenchymal hamartomas, adenomas, nodular regenerative hyperplasia, hematomas, arterial venous malformations, granulomas, and lymphangiomas [1-5,10,11]. Hemangiomas and hemangioendotheliomas are the most common vascular tumors in children and are the most frequent benign hepatic tumor seen in infants [5,11]. In small children hamartomas have been seen and are composed of mesenchymal and epithelial components often arranged to form a multicytic mass [6]. More commonly seen in older children and adolescents, focal nodular hyperplasia comprises stellate lesions of proliferating epithelial derived cells forming malformed bile ducts centrally circumscribed by a thin fibrous network of tissue that contains supplying blood vessels [3,5,12]. The diagnostic challenge is often to distinguish focal nodular hyperplasia non-invasively from an hepatic adenoma, which requires preemptive surgical resection as adenomas are at significantly higher risk for malignant transformation and/or spontaneous rupture and hemorrhage [5,7,11,12]. Nodular regenerative hyperplasia is characterized histologically by small hyperplastic nodules without a fibrous rim centered around portal tracts compressing adjacent, frequently atrophic, liver cells and sinusoids and is considered to be non-specific tissue adaptation to a heterogeneous distribution of blood flow [13,14]. Unfortunately, vascular contrast to demonstrate such features as
rim enhancement on computed tomography or magnetic resonance imaging does not conclusively distinguish focal nodular hyperplasia or nodular regenerative hyperplasia from malignant fibrolamellar hepatocellular carcinoma [5,9,12].

While the majority of benign masses may be of little consequence, morbidity and mortality can occur from benign masses [5,6]. Mass effect from a tumor can cause pain, biliary obstruction and inferior vena cava obstruction, limit lung capacity, or cause feeding difficulty [2,5,6]. Furthermore, malignant degeneration has been described from adenomas [5,12], rarely from hamartomas [6] or IHH [6,15], and possibly focal nodular hyperplasia [5]. Both IHH and hamartomas can result in fatal hemorrhage, high-output heart failure, thrombocytopenia, and disseminated intravascular coagulation (Kasabach-Merritt syndrome) [2,5,6,8]. The aim of this study was to review the clinical features, management and outcome of children diagnosed with benign liver masses at our center. These data may help illuminate an approach for the management of benign liver masses in the current era.

**RESULTS**

Over the 10 year period 1997–2009, benign masses were diagnosed in 53 children referred to our pediatric liver program. Figure 1 illustrates the various types of benign masses by frequency. The most common were IHH and focal nodular hyperplasia, which together accounted for 58% of benign masses. Table 1 presents the demographics and clinical features of children with benign masses; the mode of diagnosis, management, and length of follow-up from presentation are detailed in Table 2.

Sixteen children had IHH, 11 were incidentally found and were between 1 and 6 cm in size, including two infants with multiple IHH. The remaining five with symptomatic IHH were less than 5 months of age and had multiple masses up to 11 cm in size. Two infants developed congestive heart failure. Six children with IHH were treated with steroids. Four were listed for liver transplantation as they were refractory to treatment with steroids and/or vincristine. Three infants were transplanted by age 10 months, while the fourth died of congestive heart failure at age 4 months prior to availability of a liver graft. The fifth was a newborn with abdominal distention; evaluation with Doppler ultrasound and MRI revealed a mass up to 11 cm in largest dimension. The masses responded to medical therapy with steroids, vincristine and aminocaproic acid and did not require surgical intervention. Four of 16 (25%) children with IHH demonstrated spontaneous resolution radiologically by 4 years of age.

Children with vascular lesions in the liver that were not IHH were classified as vascular malformation. An 11 year old child with a dissecting pseudoaneurysm underwent transplantation and a newborn had a 3 cm venous malformation which regressed on follow-up imaging.

Fifteen children had focal nodular hyperplasia ranging in size from 2 to 13 cm (median 6 cm); 10 of these were incidentally found, 4 were discovered because of laboratory abnormalities, and one was secondary to an abdominal mass. The children with focal nodular hyperplasia who came to medical attention secondary to laboratory abnormalities or abdominal mass

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**PATIENTS AND METHODS**

A retrospective review of the records of all children with liver masses seen by the Pediatric Liver/Liver Transplant Program, a quaternary referral center for children with liver diseases, from 1997 to 2009 was undertaken after obtaining Institutional Review Board approval. Malignancy was excluded by evaluation of liver tumor markers and by interpretation of typical signal and enhancement characteristics seen on imaging. Histopathology, when available, was the gold standard of diagnosis. Children with preexisting chronic liver disease associated with developing benign and/or malignant liver masses such as hepatitis B or C, metabolic syndromes such as tyrosinemia, autoimmune hepatitis and/or sclerosing cholangitis, or chronic cholestatic syndromes such as progressive familial intrahepatic cholestasis were excluded from this study [5,11]. Children with indeterminant lesions, lesions without definitively benign imaging characteristics or available histopathology, were also excluded from this study. Database and statistical calculations were compiled with Excel (Microsoft, 2002).
A 15 year old girl with Turner syndrome and supplementation of growth hormone had multiple lesions up to 5 cm in size and absence of the portal vein; the lesions were diagnosed as nodular regenerative hyperplasia on histology. He had nodular regenerative hyperplasia on histology and in one case portal vein thrombosis. The child is stable after undergoing a splenorenal shunt. A 16 year old boy underwent ultrasonography for investigation of a urinary abnormality.

Table 1. Demographics and reason for presentation in children diagnosed with benign liver masses

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n (%)</th>
<th>Median age at Px (yrs) (range)</th>
<th>Gender</th>
<th>Px with abdominal mass</th>
<th>Px with lab abnormality</th>
<th>Incidental finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHH</td>
<td>16 (30)</td>
<td>0.4 (neo–18)</td>
<td>8 8</td>
<td>4</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Focal nodular hyperplasia</td>
<td>15 (28)</td>
<td>14 (neo–17)</td>
<td>12 3</td>
<td>1</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Cyst</td>
<td>6 (11)</td>
<td>2 (neo–17)</td>
<td>4 2</td>
<td>0</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Hamartoma</td>
<td>4 (8)</td>
<td>2 (neo–18)</td>
<td>1 3</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Nodular regenerative hyperplasia</td>
<td>3 (6)</td>
<td>16 (3–19)</td>
<td>2 1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Adenoma</td>
<td>2 (4)</td>
<td>12 (10–14)</td>
<td>0 2</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Vascular malformation</td>
<td>2 (4)</td>
<td>6 (neo–11)</td>
<td>0 2</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Others*</td>
<td>5 (9)</td>
<td>1 (neo–19)</td>
<td>3 2</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Total benign</td>
<td>53 (100)</td>
<td>6 (neo–18)</td>
<td>30 23</td>
<td>9</td>
<td>11</td>
<td>33</td>
</tr>
</tbody>
</table>

Px = presentation, IHH = infantile hepatic hemangioma/hemangioendothelioma, neo = neonate (birth–80 days)
*Others includes one each of polyarteritis nodosa, granuloma, hepatic hematoma, lymphangioma, and infarction

Table 2. Mode of diagnosis and treatment of children with benign liver masses

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total</th>
<th>Diagnosed by imaging</th>
<th>Diagnosed by biopsy</th>
<th>Diagnosed at resection or transplant</th>
<th>Observed</th>
<th>Medical treatment</th>
<th>Surgical treatment (includes Tx)</th>
<th>Median follow-up (mos) (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHH</td>
<td>16</td>
<td>15</td>
<td>1</td>
<td>0</td>
<td>9</td>
<td>7</td>
<td>3</td>
<td>8 (1–81)</td>
</tr>
<tr>
<td>Focal nodular hyperplasia</td>
<td>15</td>
<td>6</td>
<td>4</td>
<td>5</td>
<td>8</td>
<td>0</td>
<td>7</td>
<td>16 (4–48)</td>
</tr>
<tr>
<td>Cyst</td>
<td>6</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>4 (2–60)</td>
</tr>
<tr>
<td>Hamartoma</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>30 (4–68)</td>
</tr>
<tr>
<td>Nodular regenerative hyperplasia</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>9 (2–25)</td>
</tr>
<tr>
<td>Adenoma</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3 (2–3)</td>
</tr>
<tr>
<td>Vascular malformation</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>16 (12–20)</td>
</tr>
<tr>
<td>Others*</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>5 (1–40)</td>
</tr>
<tr>
<td>Total benign</td>
<td>53</td>
<td>31</td>
<td>7</td>
<td>15</td>
<td>27</td>
<td>9</td>
<td>22</td>
<td>9 (1–81)</td>
</tr>
</tbody>
</table>

IHH = infantile hepatic hemangioma/hemangioendothelioma
*Others includes one each of polyarteritis nodosa, granuloma, hepatic hematoma, lymphangioma, and infarction

detection were younger at presentation (median age 11 years) compared to those with incidentally found focal nodular hyperplasia (median age 14 years). The median size of focal nodular hyperplasia masses was 7 cm (range 5–12 cm) for symptomatic children compared to 5 cm (range 3–13 cm) in incidentally found focal nodular hyperplasia. A 3 year old with esophageal variceal bleeding and history of premature birth and umbilical line placement was found on imaging to have portal vein thrombosis. He had nodular regenerative hyperplasia on histology and a subsequent MRI demonstrated numerous 1 cm lesions in the liver. The child is stable after undergoing a splenorenal shunt. A 15 year old girl with Turner syndrome and supplementation with progesterone and growth hormone had multiple lesions up to 5 cm in size and absence of the portal vein; the lesions were diagnosed as nodular regenerative hyperplasia on histology.

The tumor was an incidental finding in 33 (62%) of the 53 children imaged for other reasons. Reasons for these imaging investigations included acute non-hepatic gastrointestinal processes (e.g., appendicitis) suspected in 12 cases, urinary issues such as infection or hematuria (n=7), suspected non-hepatic congenital abnormalities (n=6), investigation for ovarian cysts or torsion (n=3), and routine prenatal screening (n=2); further cases were identified for one each of viral respiratory process, monitoring of a cardiac transplant patient, and screening in a child with a family history of adrenal cancer, respectively. In none of these cases were the symptoms related to the tumors.

A male infant had an enlarged liver noted on prenatal ultrasound, and on postnatal imaging a suspicion for multifocal hepatoblastoma was raised. A resection at age 4 weeks revealed mesenchymal hamartoma and this boy was thriving at 4 months of age. Three children of various ages with a history of hydronephrosis, hematuria, and a sibling with adrenal tumor respectively, had hepatic lesions 2–6 cm in size uncovered during imaging investigations. Upon resection they had ciliated cystic hamartomas that did not recur. A 16 year old boy underwent ultrasonography for investigation of a urinary problem.
tract infection and was found to have a 12 cm hepatic cyst. Suspicion for echinococcal infection prompted treatment with albendazole. Surgical resection and pathological examination was not specific for an echinococcal origin of the cyst.

Laboratory abnormalities prompted abdominal imaging in 11 children (21%); 10 children had imaging done for abnormal liver function tests and one had thrombocytopenia. Radiographic findings were diagnostic in 31 (58%) of the 53 children. Definitive histological diagnosis was made in the remaining 22 (42%), either from imaging guided/laparoscopic biopsies in 7 children (13%) or from surgical resection (including liver transplantation) in 15 (28%). Of the 53 children with benign liver lesions, 27 were under observation while 17 had masses resected. Medications targeting masses were used in nine and liver transplantation was performed in four (three IHH, one vascular malformation). The only death occurred in a child with multifocal IHH unresponsive to medical management and prior to liver transplant availability.

For the 27 children whose benign liver lesions were observed without intervention, clinical follow-up information was available for a median duration of 9 months (range 1 month to 5 years). Four children who were observed without intervention had complete resolution of their tumor, while 3 had imaging studies showing tumor regression, and 14 children had lesions that were unchanged. None of these observed lesions were known to increase in size, although for six children no follow-up imaging information was available.

Almost all of our patients were referred from the New York/New Jersey regional area and ethnicity was representative of the diversity of the region, with no predominance for a particular tumor. Based on our experience, we devised an algorithm for the management of suspected benign pediatric liver masses [Figure 2] to better guide management at other regional referral centers with expertise in the diagnosis and management of pediatric liver lesions.

**Figure 2.** Algorithm demonstrating clinical approach to benign pediatric liver lesions

*The evaluation of lesions presumed to be malignant is excluded. FNH = focal nodular hyperplasia, OLT = orthotopic liver transplant.*
DISCUSSION

The present study is the largest single-center study documenting the clinical features, diagnosis, management and outcome in children with benign liver masses. Although rare in children, benign tumors affect approximately 20% of the U.S. population [10] and constitute a significant number of outpatient referrals annually in pediatric practice. In the present work, an approach to managing these lesions as non-invasively as possible, using the latest imaging techniques is presented and an algorithm developed to illustrate our approach.

The majority of benign masses in our series were incidentally found and asymptomatic, compared to the presence of symptoms in over 70% in other reported series [1,2]. This may be secondary to the increased use of improved imaging modalities detecting masses on studies performed for unrelated indications. In a study examining 155 adults with benign liver tumors [7], nearly half were symptomatic and only 10% had abnormal liver function tests in comparison to 22% children in our study. There is a report of more than 300 children with histologically diagnosed benign liver tumors, but this was pathology based and unfortunately no information on clinical presentation or outcome was provided in that series [16]. The other major study describing benign lesions in children is from more than two decades ago, and given that radiological methods of examination were not that advanced between 1950 and 1981, many of the 48 children had their lesions diagnosed after developing major complications and 13 of the 48 were diagnosed postmortem [1].

IHH was the most common benign liver lesion in our series. It may be suggested by visible cutaneous strawberry hemangiomas in an infant with a liver mass [9]. Associated hypothyroidism may also suggest that the mass is IHH, and previous reports suggest screening for hypothyroidism [11,17,18] as shown in our algorithm. All four of the infants listed for liver transplantation had evidence of hypothyroidism. A large rapidly growing IHH can cause high output heart failure, arteriovenous shunting, massive hepatomegaly and Kassabach-Merritt syndrome [2,8]. The latter refers to a localized intravascular coagulopathy with thrombocytopenia [2]. Elevated liver enzymes with or without jaundice may result from biliary and/or vascular obstruction by the lesion [9]. Diagnostic options to identify IHH include Doppler-enhanced sonoigraphy and contrast-enhanced CT or angiographic techniques [5,17]. Ultrasound without Doppler might only differentiate cystic masses from solid ones, and in one series IHH appeared as if solid in all six children [1]. MRI with contrast enhancement may provide the best identification of flow characteristics and surrounding vascular structures [17], with lower false positive rates for hepatocellular carcinoma and less ionizing radiation risk than CT [11]. For pediatric liver masses where a definitive diagnostic characterization by Doppler ultrasound is not achieved, our algorithm [Figure 2] suggests that referral to a center where MRI is available be strongly considered secondary to the superiority of MRI over CT [11]. Radiological findings may not always reflect true liver pathology, and in a study that initially identified 62 children with radiological diagnoses of IHH, 3 had malignant tumors based on tissue pathology [17].

Corticosteroids are the mainstay of treatment of IHH [5,17]. More recently propranolol has been used successfully in the initial treatment of IHH [18]. Second-line therapy includes hepatic artery ligation and transcatheter embolization [5,17], surgical excision [1,2,5,17], and rarely liver transplantation [5,11,19]. Observation with periodic re-imaging may be appropriate for asymptomatic IHH [9], as was utilized for the majority of 16 cases of IHH in our series [Table 2], with 4 (25%) demonstrating spontaneous resolution by age 4 years. Complete spontaneous regression of benign liver tumors can occur, including small focal IHH [5,20], inflammatory pseudotumor/myofibroblastic tumor [20] and peliosis hepatic [21].

Oral contraceptives are associated with the development of focal nodular hyperplasia, adenosomas and nodular regenerative hyperplasia [2,5,20]. Only two of the patients in this series were on hormonal supplementation. This included a 14 year old adolescent female on a low dose oral contraceptive pill, with a 2 cm lesion diagnosed as focal nodular hyperplasia based on imaging characteristics. The oral contraceptive was stopped and the lesion has been managed expectantly without any significant enlargement. The other adolescent on hormonal supplementation, a 15 year old girl with Turner syndrome and supplementation with progesterone and growth hormone, had multiple lesions up to 5 cm in size and absence of the portal vein; the lesions were diagnosed as nodular regenerative hyperplasia on histology. In focal nodular hyperplasia many masses, but not all, demonstrate the classic finding of a central scar [5,12]. Adenomas frequently display a heterogeneous appearance due to intraslesional fat and/or hemorrhage [12]. Accurate diagnostic differentiation of adenoma from focal nodular hyperplasia is important because adenomas may rupture and bleed or undergo malignant transformation into hepatocellular carcinoma, while focal nodular hyperplasia may usually be observed with expectant management [3,12].

MRI with gadobenate dimeglumine (MultiHance, Bracco Diagnostics, Princeton, NJ, USA) intravenous contrast provides accurate discrimination of focal nodular hyperplasia from adenoma for at least 97% of adults, as focal nodular hyperplasia enhances at 1–3 hours on delayed imaging phase because of the presence of bile ductules [12]. The telangiectatic type of focal nodular hyperplasia has multiple dilated blood spaces near the center of the lesion without significant fibrosis; it may have an increased potential for malignant deterioration and hemorrhage similar to adenomas and possibly should be managed aggressively [22]. Although adenomas may spontaneously disappear [20], our algorithm recommends surgical resection
of adenomas due to the risks of malignant degeneration [9,12] or hemorrhage after rupture [5,12].

Hamartomas are the second most common benign tumors in infants and are thought to be the result of ductal plate malformations, vascular insult, toxic injury or neoplasia [6]. Lesions may either be predominantly stromal or cystic with imaging studies showing a multilocular, multicystic mass with low density cysts separated by dense septae [5,6]. Similar to our experience in all four children with hamartoma, imaging findings are usually inconclusive, with the hamartoma diagnosed only after biopsy or resection to exclude the possibility of malignancy [5,6,9]. Solitary cystic lesions have previously been described to occur in children of all ages, are best demonstrated by ultrasound, and are usually asymptomatic [6] – all findings that are consistent with our series.

Histological differentiation can be difficult, and core biopsy, rather than fine needle aspiration, is recommended [6]. Lesions should be at least 2 cm in diameter and well visualized by the imaging modality used to facilitate biopsy. Major vascular structures may prevent safe passage of the needle in image-guided biopsy and make operative biopsy or resection difficult [23]. In a study of 36 pediatric liver lesions that underwent CT or sonographically guided fine needle aspiration, 53% had histopathology consistent with malignancy, 36% initially were classified as benign, and 11% had indeterminate pathology [4]. Of the 53 children with benign liver tumors followed by our center, 4 (8%) were transplanted, 3 for IHH and one for vascular malformation. While this high percentage may reflect that children referred to a quaternary referral center frequently require more advanced care, cases of benign liver tumors requiring transplantation are well documented. A recently published review mentions that in the United Network for Organ Sharing database during the 20 year period 1987–2007, there are 39 reported cases of liver transplantation for IHH, 7 for adenoma, 2 for arteriovenous malformation and 2 for hamartoma [11]. Details of 29 pediatric and adult patients with benign tumors who have undergone liver transplantation have also been published [10,19,24,25]. An additional 112 pediatric and adult patients have had liver transplantation for polycystic liver disease [10].

The spectrum of benign liver lesions in pediatrics is similar to that seen in adults. Benign liver masses are of diverse etiologies and are often found incidentally. IHH and focal nodular hyperplasia were the most common lesions in the present series. Diagnosis was made radiologically in over 50% and histologically in the rest. The devised algorithm may be helpful in the management of children presenting with benign liver masses. Advanced imaging modalities together with improved surgical techniques, intensive care facilities, and the option of liver transplantation have led to a substantial improvement in the diagnosis and treatment of benign liver masses occurring in children.

Corresponding author:
Dr. I.N. Kochin
Pediatric Liver and Liver Transplant Program, Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1104, New York, NY 10029, USA
Phone: (1-212) 659-8060
Fax: (1-212) 659-8066
e-mail: israel.kochin@mssm.edu

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