Case Report

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Hepatic Lymphangiomatosis Mimicking Polycystic Liver Disease

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Hepatic lymphangiomatosis is a rare disorder characterized by cystic dilatation of the lymphatic vessels in the hepatic parenchyma. It can occur in the liver alone, in the liver and spleen, or in multiple organs. Clinically, diagnosis can be difficult because of the rarity and protean manifestations of this disorder. We describe a 53year-old woman with hepatic lymphangiomatosis in whom polycystic liver disease had been previously diagnosed. In addition, we review 12 cases of hepatic, splenic, and hepatosplenic lymphangiomatosis with or without

Polycystic liver disease (PLD) is a term that specifically refers to the presence of multiple cysts in the hepatic parenchyma and is typically reserved for use in relation to a heritable disease most commonly associated with cysts in other organs. PLD usually occurs with autosomal dominant polycystic kidney disease (ADPKD), both PKD-1 and PKD-2.¹ Rarely, members of families with ADPKD will have hepatic cysts independent of renal cysts, and small numbers of families have been described who have autosomal dominant PLD (ADPLD) without renal cysts.^{2,3} Hepatic cysts have also been documented to occur with von Hippel-Lindau (vHL) disease,^{4,5} tuberous sclerosis complex (TSC),⁶ and orofaciodigital syndrome type I (OFD-I).⁷ Herein we describe a woman with systemic lymphangiomatosis. The clinical manifestations of this rare condition can be confused with PLD.

REPORT OF CASE

A 53-year-old woman was referred to our institution for medical assessment. Her past medical history included petit mal seizures during childhood, a vaginal hysterectomy for benign leiomyomas when she was 32 years old, a bilateral oophorectomy for ovarian cysts when she was 37, and recurrent skin lesions. Biopsy specimens from these lesions had never been obtained, but cryotherapy had been

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systemic lymphangiomatosis and discuss the differential diagnosis.

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ADPKD = autosomal dominant polycystic kidney disease; ADPLD = autosomal dominant polycystic liver disease; CTs = computed tomograms; OFD-I = orofaciodigital syndrome type I; PLD = polycystic liver disease; TSC = tuberous sclerosis complex; US = ultrasonogram; vHL = von Hippel-Lindau

successful. In 1986, at 43 years of age, the patient had a mass resected from her neck. Pathologic study revealed the presence of benign lymphoid tissue and cystic structures. In 1989, the patient sought medical advice because of respiratory symptoms. A chest roentgenogram revealed a 5-mm nodule in the lower lobe of her right lung. Computed tomograms (CTs) of the chest and abdomen disclosed two pulmonary nodules and multiple cysts in the liver and spleen. Serial chest roentgenograms demonstrated the lesions to be stable. In 1992, the patient had development of a recurrent neck mass that was consistent with a lymphangioma on a CT (Fig. 1).

In 1994, the patient experienced abdominal fullness and increased abdominal girth. An ultrasonogram (US) and CT (Fig. 2) of the abdomen again demonstrated cysts in the liver and spleen. No cysts were detected in the kidneys. A CT of the chest revealed that the pulmonary nodules had increased in number and size. These nodules had negative attenuation values, likely due to partial volume averaging of adjacent lung tissue (Fig. 3). The patient underwent partial resection of the liver and fenestration of multiple cysts, with a marked reduction in liver size and good preservation of liver parenchyma (Fig. 4). On histologic examination of the resected tissue, the process was thought to be consistent with PLD. For a better definition of the pulmonary process, a transthoracic needle biopsy was attempted. Not enough material was obtained for diagnosis; however, after aspiration, a CT revealed that a small cystic cavity was remaining, a suggestion that the lesion could in fact be a lymphangioma. At that time, pulmonary function testing revealed a reduction in forced vital capacity, forced expiratory volume, and diffusing capacity. The neck mass noted in 1992 was resected 4 years later, and pathologic

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Fig. 1. Computed tomogram of neck with use of contrast medium, showing low-density cystic mass (*arrow*) in left side of neck, consistent with lymphangioma.

examination confirmed the diagnosis of a lymphangioma (Fig. 5).

On admission to our institution, the patient had no medical complaints. Her blood pressure was normal, and physical examination findings were notable only for mild hepatomegaly. Results of thorough dermatologic and ophthalmologic examinations were unremarkable. Laboratory studies revealed normochromic, normocytic anemia; a slightly increased alkaline phosphatase level of hepatic origin; a normal creatinine value; and normal findings on urinalysis. Chest roentgenography demonstrated a minimal infiltrate in the right base of the lung, and a small sclerotic area in the upper shaft of the right humerus was identified on a skeletal scan. A CT of the chest demonstrated numerous pulmonary nodules, similar to those detected on previous CTs. A CT of the abdomen again revealed hepatosplenomegaly caused by pronounced cyst formation in both organs. No structural abnormalities were noted on magnetic resonance imaging of the head. Colonoscopy revealed no hamartomatous polyps.

The family history was notable in that the patient's mother had undergone a salpingo-oophorectomy for ovarian cysts, but she had no history of cysts in other organs. No other person in the pedigree had a history of cystic disease. Abdominal US of the patient's mother and daughter showed no renal or hepatic cysts or ovarian cysts in the patient's daughter. Findings on a chest roentgenogram and contrast-enhanced CT of the abdomen of the patient's son were normal.

A review of the tissue from the cystic neck mass that had been resected in 1996 confirmed the diagnosis of lymphangioma. With immunoperoxidase staining, the lining cells were positive for factor VIII and negative for



Fig. 2. Computed tomograms of liver, spleen, and kidneys, demonstrating extensive cyst formation throughout liver and spleen, as well as fluid-debris levels (*arrows*) in several cysts in liver. Note absence of cysts in kidneys.



Fig. 3. Magnified view of right lung on chest computed tomogram, demonstrating multiple pulmonary nodules in right lung. Large nodule has negative attenuation value (-165 Hounsfield unit), likely due to partial volume averaging of adjacent lung tissue.

cytokeratin, findings that support a diagnosis of lymphangioma. A review of histologic specimens from the prior liver resection revealed multiple haphazardly arranged, thin-walled cysts filled with clear material consistent with lymph. The lining consisted of attenuated endothelial cells positive for factor VIII and negative for cytokeratin, similar to the cells in the neck lesion (Fig. 6). Soft tissue in the neck region of the gallbladder contained a few dilated lymphatic spaces. These pathologic findings, in the context of the woman's clinical history, are consistent with the diagnosis of diffuse lymphangiomatosis.

DISCUSSION

Our patient had diffuse lymphangiomatosis with prominent hepatic and splenic involvement. On imaging studies, the appearance of hepatic lymphangiomatosis may resemble that of PLD. In our patient, PLD had been diagnosed, and this diagnosis was not changed, even after partial liver resection and fenestration. Nevertheless, several unusual features suggested a different diagnosis—specifically, the nature of the extrahepatic manifestations, the absence of a family history of polycystic kidney or liver disease, and subtle abnormalities on a US and CT of the liver.

PLD can occur in association with ADPKD, both PKD-1 and PKD-2, as well as a genetically distinct entity without renal involvement (ADPLD).^{2,3} Extrarenal manifestations of ADPKD, such as mitral valve prolapse and intracranial aneurysms,⁸ were not present in our patient. Splenic cysts are an extremely rare manifestation of ADPKD, occurring in 0.5% of patients. The severity of splenic involvement in



Fig. 4. Computed tomograms of liver, spleen, and kidney after partial hepatectomy and fenestration of cysts, demonstrating marked reduction in number and size of liver cysts and preservation of normal liver parenchyma.

our patient, however, would be exceedingly rare in association with ADPKD.⁹ In addition, the presence of a recurrent neck mass and pulmonary hamartomas, which are not associated with ADPKD or ADPLD, suggest a different diagnosis.

Although PKD-1 and PKD-2 have a moderately high spontaneous mutation rate and absence of a family history in patients with ADPKD or ADPLD is not rare,8 the absence of a family history of these diseases in a patient with multiple renal or hepatic cysts raises the possibility of other diagnoses, such as TSC, vHL disease, and OFD-I. Because of high spontaneous mutation rates and lower reproductive potentials, patients with TSC and vHL disease have new mutations more often than do those with ADPKD or ADPLD.5.6 Nevertheless, hepatic cysts occur more rarely in these diseases. The pulmonary hamartomas or lymphangiomas in our patient differed from the pulmonary lymphangioleiomyomatosis that occurs in patients with TSC.6 Although extrapulmonary lymphangiomatous cysts can occur in patients with TSC10 and our patient had a history of petit mal seizures during childhood, she had no other manifestations suggestive of TSC. Central nervous system, ophthalmologic, pancreatic, or renal features to suggest a diagnosis of vHL disease were absent,4.5 as were the characteristic oral, facial, and digital malformations of OFD-I.7

Most of the cysts in our patient were highly echogenic on US, and many contained fluid-debris levels, which are optimally demonstrated on a CT (Fig. 2). The US and CT characteristics of the cystic lesions in her liver are common in PLD and may reflect a previous cyst hemorrhage or infection. Nevertheless, in our experience, the number of cystic lesions with this appearance in our patient is unusual with PLD. A similar appearance of such lesions was described in a previous report of hepatic lymphangiomatosis and probably reflects the different composition of the fluid in these cystic lesions in comparison with that of the fluid in the cysts of a polycystic liver.¹¹

In our patient, the presence of a cervical lymphangioma, multiple pulmonary lymphangiomas, and extensive cystic changes of the spleen suggest a diagnosis of systemic lymphangiomatosis. The ovarian cysts previously resected probably represented lymphatic cysts. The diagnosis of systemic lymphangiomatosis was confirmed by histologic evaluation of the liver and the cervical mass. The cysts in ADPKD, in contrast to those in lymphangiomatosis, are lined with biliary epithelium rather than with endothelium. Occasionally, the two entities may be difficult to distinguish, however, because the epithelium in larger cysts in ADPKD may become markedly attenuated (mimicking endothelium) and the cysts in ADPKD often contain clear fluid (mimicking lymph). A thorough search for recognizable epithelium in the smaller cysts will facilitate accurate



Fig. 5. Pathologic features of lymphangioma in neck. Series of fenestrations (*arrows*) divide lymph-filled cysts. Cysts are lined with barely visible, attenuated endothelium. (Hematoxylin-eosin; original magnification, x40.)

identification of ADPKD in most cases, although equivocal cases may necessitate immunohistochemical analysis. The cysts in ADPKD will be positive for keratin and negative for factor VIII, whereas those in lymphangiomatosis will be positive for factor VIII and negative for keratin.

Lymphangiomatosis is a rare, sporadic disorder characterized by cystic lymphangiomas involving multiple organs.^{12,13} Systemic lymphangiomatosis, also termed "systemic cystic angiomatosis" by Seckler and colleagues,¹² represents a generalized disorder of the lymphatic system in conjunction with cyst formation, found either alone or in combination, in bone, mediastinum, lung, pleura, liver, spleen, kidney, supraclavicular soft tissues, and axilla. The cystic cavities vary in size, from microscopic to several



Fig. 6. Photomicrograph of hepatic lymphangiomatosis. Multiloculated cysts were present in haphazard fashion throughout resected liver. Cysts are lined with thin, attenuated endothelial lining (*arrows*) and contain lymph, which is barely visible as slightly granular gray material. (Hematoxylin-eosin; original magnification, x400.)

centimeters in diameter.¹³ The formation of cystic lymphangiomas is thought to be due to sequestration or obstruction of lymphatic vessels during embryogenesis. The cause is unknown. Cystic angiomatosis of bone has been reported in multiple members of the same family, and pulmonary cystic lymphangiomas have been described in siblings who died during the neonatal period. Familial disease has not been reported in the rest of the patients with lymphangiomatosis. Therefore, minimal evidence supports the theory that lymphangiomatosis is an inherited disease.

Clinically, the disorder can be classified as systemic, hepatosplenic, or purely splenic or hepatic. In a review of the literature, we identified 12 cases of lymphangiomatosis involving the liver or spleen (or both) with or without other organ involvement. Two additional cases were excluded because the disease seemed to be due to trauma14 or thoracic duct ligation for primary chylopericardium.15 Of the 12 cases, 3 were isolated liver disease,^{11,16} 3 were isolated splenic disease,17-19 1 involved both the liver and the spleen,20 and 5 involved multiple organs, including the liver or the spleen (or both).^{13,19,21-23} Gender distribution is similar. Age at onset of disease ranges from birth to the seventh decade of life; however, isolated solid organ involvement seems to occur in patients older than 25 years of age. Initial symptoms are usually related to the mass effect caused by the enlarged organs, but in two cases, the lesions were asymptomatic. Our patient had hepatosplenic and pulmonary lymphangiomas, cystic lymphangioma, and presumed involvement of the uterus and ovaries. Although the pulmonary lesions caused mild restrictive physiologic changes, as shown on pulmonary function testing, our patient was asymptomatic. The liver lesions, however, caused significant clinical problems, as has been previously described. Even though the prognosis of systemic lymphangiomatosis has been reported to be poor relative to isolated bone lymphangiomatosis,21 our patient is doing well after partial hepatectomy, with stable liver and pulmonary function.

Cystic lymphangiomas necessitate treatment only if symptoms occur. Treatment typically consists of surgical resection of cystic organs or, if not possible, fenestration of large cysts.^{15,24} Splenectomy tends to result in relief of symptoms and in resolution of anemia and thrombocytopenia in patients with hypersplenism. Therapeutic options for liver cysts are the same as those for PLD. These options are as follows: observation if the patient is free of pain and has no anatomic complications caused by cyst size or site; cyst fenestration and partial liver resection if the cysts are isolated to discrete segments of the liver; and transplantation if hepatocellular function is sufficiently compromised and partial hepatectomy is not possible because of diffuse organ involvement.23 Our patient had undergone successful partial hepatectomy with relief of symptoms and marked sustained reduction in liver size before her referral to our institution.

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