

Retroperitoneal lymphangioma: A report of 2 cases and a review of the literature regarding the differential diagnoses of retroperitoneal cystic masses

MARIACRISTINA DI MARCO, ELISA GRASSI, SILVIA VECCHIARELLI,
SANDRA DURANTE, MARINA MACCHINI and GUIDO BIASCO

Department of Experimental, Diagnostic and Speciality Medicine, University of Bologna,
Sant'Orsola-Malpighi Hospital, I-40138 Bologna, Italy

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Abstract. Cystic lymphangioma is a type of benign tumor originating from the lymph vessels. The tumor commonly occurs in childhood, in the head or neck regions, and retroperitoneal localization and presentations in adulthood are rare. Determining a pre-operative diagnosis is often challenging, and in the majority of cases, a diagnosis is only possible subsequent to the histological examination of the surgical specimen. A radical resection is the recommended treatment for cystic lymphangioma, and recurrence is usually due to an incomplete excision of the mass. The present study reports 2 cases of cystic lymphangioma, localized in the pancreatic gland and duodenal wall respectively, which were treated with surgical resection. The study also briefly reviews the literature regarding the differential diagnosis of retroperitoneal cystic masses.

Introduction

Lymphangioma is a rare benign neoplasm, described for the first time by Koch in 1913 (1). The tumor is rare, and its exact incidence is unknown (1). It originates from a congenital malformation of the lymphatic channels, due to an obstruction of the lymphatic ducts, and results in lymphangiectasia. The disease most frequently occurs in the pediatric age group, and ~90% of cases are diagnosed prior to 2 years of age. The most common sites of the tumor are regions of the neck, head and axillae, while abdominal localization is rare (1).

The majority of abdominal lymphangiomas, which account for 1% of all lymphangioma cases, are localized in

retroperitoneal or mesenteric sites, and pancreatic localization is rare. They are usually symptomatic and found accidentally (2). In symptomatic cases, the clinical presentation includes abdominal pain and distension. Symptoms may rarely be associated with complications, including intracystic bleeding, infection, cyst rupture or compression of adjacent organs (3). Diagnostic techniques include computed tomography (CT), magnetic resonance imaging (MRI) and endoscopic ultrasound with cyst fluid fine-needle aspiration, however, a definitive diagnosis of cystic lymphangioma is typically achieved by histological examination subsequent to surgery or exploratory laparotomy (3). Radical surgery is the recommended treatment for abdominal lymphangiomas, therefore, recurrence is rare and usually occurs due to an incomplete resection. Conservative methods, including aspiration, cyst enterostomy and peritoneal marsupialization, are now obsolete due to the high rate of recurrence (2).

The present study reports 2 cases of retroperitoneal cystic lymphangioma that were treated by radical surgical resection and briefly reviews the literature regarding the differential diagnoses of retroperitoneal cystic masses.

Case report

Case 1. In July 2012, an asymptomatic 43-year-old man, with no history of pancreatic or other gastrointestinal anomalies, received an abdominal computed tomography (multidetector CT using a 16-detector row system; Siemens AG, Munich, Germany) scan at Sant'Orsola Malpighi Hospital (Bologna, Italy) due to the accidental finding of hypertransaminasemia during a routine checkup. CT images were acquired using a triphasic scanning technique, with scan delays of 35, 80 and 180 sec for the early arterial, portal venous and late portal venous phases, respectively, following intravenous injection of 150 ml of iodinated contrast solution (Xenetrix®; Guerbet, Roissy CdG Cedex, France), at a rate of 2-3 ml per sec. Multiplanar reconstructions were used to identify vascular anatomy. Response Evaluation Criteria In Solid Tumors were used to evaluate anatomic disease staging. Analysis was performed using tumor size (in cm) and attenuation coefficient (in Hounsfield Units) of the mass on the CT images. The CT

Correspondence to: Miss. Elisa Grassi, Department of Experimental, Diagnostic and Speciality Medicine, University of Bologna, Sant'Orsola-Malpighi Hospital, 9 Massarenti Street, I-40138 Bologna, Italy
E-mail: elisa.grax@gmail.com

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scan revealed the presence of a 82x73 mm voluminous multi-chamber cystic formation with a fluid content in the left side of the abdomen, which extended from the large curvature of the stomach to the pancreatic tail, with no infiltration of the adjacent parenchyma. The cystic fluid was aspirated for cytological characterization using CT-guided needle aspiration, and the presence of serous material with small, mature and atypical lymphocytes and the absence of epithelial and neoplastic cells was determined. Due to the risk of malignancy, surgery was planned. A distal splenopancreasectomy was performed to remove the adherent cystic lesion. Specimens were prepared for routine histopathological examination using hematoxylin and eosin staining. Briefly, sections were fixed in 4% paraformaldehyde (Sigma-Aldrich) and paraffin-embedded (Merck Millipore, Darmstadt, Germany). Sections (7- μ m) were then cut and stained with hematoxylin and eosin (Sigma-Aldrich, St. Louis, MO, USA) and observed under a light microscope (Eclipse E800; Nikon Corporation, Tokyo, Japan). The histological examination of the lesion revealed multichamber cysts that were formed from epithelial elements. For immunohistochemical analysis, the sections were deparaffinized (100% xylene for 2 min, three times), rehydrated (100% ethanol for 2 min, three times; 95% ethanol for 2 min, three times; 80% ethanol for 2 min, three times; 50% ethanol for 2 min, three times; distilled water for 2 min, two times) and boiled in citric acid (Sigma-Aldrich) for 20 min. All slides were cooled with running tap water and equilibrated for 20 min at room temperature (RT). Endogenous peroxidase activity was blocked using 3% hydrogen peroxide for 15 min at RT, followed by 2 washes with water and phosphate-buffered saline (PBS) at room temperature for 3 min. The sections were then incubated with bovine serum albumin and skimmed milk in PBS (blocking solution) for 1 h. Next, the sections were incubated with monoclonal mouse anti-human CD31 (catalog no., 89C2; Cell Signaling Technology, Inc., Danvers, MA, USA) or monoclonal mouse anti-human HMB-45 (catalog no., MA5-16712; Thermo Fisher Scientific, Inc., Waltham, MA, USA) primary antibodies at a dilution of 1:100 for 16 h at 4°C. Sections were washed twice in PBS at room temperature for 3 min and the antibody signals were detected by secondary antibodies included in the Histofine Immunohistochemical staining kit (catalog no. 414151F; Nichirei Biosciences Inc., Tokyo, Japan) according to the manufacturer's instructions. The sections were counterstained with hematoxylin and observed under a light microscope (Eclipse E800; Nikon Corporation). Immunohistochemically, the endothelial cells lining the surface of the cystic space expressed cluster of differentiation (CD)31, but not monoclonal mouse anti-human melanosome, clone HMB-45 (HMB-45), which is compatible with a diagnosis of cystic lymphangioma originating from the pancreatic lymph vessels. The post-operative course was uneventful. The patient was enrolled in a clinical and instrumental follow-up program. Clinical follow-up and radiological investigations with alternating abdominal ultrasound and CT scans were performed every 6-8 months for the first 2 years following surgery, and annually for the subsequent 3 years. The patient remains alive and free from disease at 3 years and 4 months after surgery.

Case 2. In October 2012, a 29-year-old man was hospitalized at Sant'Orsola Malpighi Hospital (Bologna, Italy) due to the

progression of anemia. During the patient's hospitalization, a gastroscopy was performed to assess the cause of the anemia, which revealed a circumferential lesion in the third region of the duodenum. The biopsy that was performed during the endoscopy examination revealed the presence of intestinal lymphangiectasia. A CT scan (multidetector CT using a 16-detector row system; Siemens AG) demonstrated the presence of thickened jejunal loops with signs of stenosis and hypovascularization. Positron-emission tomography with 18F-fluorodeoxyglucose (¹⁸F-FDG PET) revealed the presence of abdominal tissue with medium glucose metabolism in the duodenal-jejunal region. The patient underwent surgery, and during the laparotomy, the voluminous cystic mass located in the third region of the duodenum was identified, which demonstrated intraluminal and exophytic development in the mesenteric region. The patient underwent an *en bloc* resection of the third region of the duodenum, extending to the jejunum and the fourth region of the duodenum. To re-establish gastrointestinal continuity, a side-to-side jejuno-duodenostomy was performed. Tissues were prepared for histological examination as described previously for case 1. The histopathological examination confirmed the pre-operative diagnosis of cystic lymphangioma, and revealed that the proliferation of lymphatic and blood venous vessels extended to the duodenal wall and perivisceral adipose tissue. The lymphatic component was filled with eosinophilic serous material. The post-operative course was uneventful. The patient was followed up with clinical and radiological controls. Clinical follow-up and radiological investigations with alternating abdominal ultrasound and CT scans were performed every 6-8 months for the first 2 years following surgery, and annually for the subsequent 3 years. The patient remains alive and free from disease at 3 years and 3 months after surgery.

Discussion

Despite the rare incidence of the disease, cystic lymphangioma possesses differential diagnostic criteria compared with other retroperitoneal cystic masses. The benign tumor originates from the abnormal development of the lymphatic structures that are commonly localized in the head and neck regions (75% of cases) or the axilla region (20% of cases), and usually occurs in the pediatric age group. An abdominal localization and presentation in adulthood is extremely rare. In general, abdominal lymphangioma occurs in the mesenteric region; occurrence in the mesocolic and retroperitoneal regions, and the walls of the small and large intestines are rarer (4).

Pancreatic cystic lymphangioma is a type of retroperitoneal lymphangioma, which only represents 0.2% of all pancreatic tumors and possesses differential diagnostic criteria compared with other cystic pancreatic and extra-pancreatic neoplasms, or compared with non-neoplastic lesions. Unlike the lymphangiomatosis of retroperitoneal origin, which occur more frequently in men, pancreatic lymphangiomatosis is more common in women (male:female ratio, 16:29), and are localized preferentially in the pancreatic body, not in the head (5,6). The etiology of this finding remains unclear. According to the most popular theory, these lymphangiomatosis develops from a congenital malformation of the lymphatic channels that dilates, resulting in the formation of

Table I. Type and characteristics of neoplastic retroperitoneal cystic neoplasms.

Type of cystic neoplasm	Epidemiological and clinical features	Morphologic features on ultrasound and CT scan	Malignant potential	First author
Cystic teratoma	Female gender, new-borns, usually asymptomatic	Complex mass containing a well-circumscribed fluid component, adipose tissue and calcification	Benign	Davidson <i>et al</i> (18)
Cystic mesothelioma	Female gender, abdominal pain, not associated with prior asbestos exposure	Thin-walled, multilocular cystic lesion	Benign	Li <i>et al</i> (19)
Müllerian cyst	Female gender, childbearing age, obese women with menstrual irregularities receiving hormonal therapy	Unilocular or multilocular thin-walled cyst that contains clear fluid	Benign	Lee <i>et al</i> (20)
Epidermoid cyst	Female gender, middle age, asymptomatic or symptoms due to a local mass effect (usually presacral retroperitoneal localization)	Thin-walled, unilocular cystic mass with fluid attenuation	Benign	Yang <i>et al</i> (21)
Tailgut cyst	Female gender, middle age	Well-defined multicystic mass with various attenuation values, between water and soft tissue, and rare thin calcifications	The majority are benign, but malignant change is possible	Johnson <i>et al</i> (22)
Bronchogenic cyst	Male or female gender, congenital anomalies, asymptomatic or symptoms due to secondary infection, perforation or compression	Rounded well-circumscribed hypoattenuating, or hyperattenuating with protein content, cyst without enhancement	Benign. Malignant degeneration is extremely rare	Murakami <i>et al</i> (23)
Cystic changes in solid neoplasms	Other types of solid retroperitoneal neoplasms may be cystic, including paraganglioma, neurogenic tumors, leiomyosarcoma and GISTs	Radiological images are particular to each type of tumor and the associated cystic component	Malign	Rha <i>et al</i> (24), Ogoose <i>et al</i> (25), MacVicar <i>et al</i> (26) and Chen <i>et al</i> (27)
Pseudomyxoma retroperitonei	Male or female gender, any age, palpable mass and abdominal pain due to compression of adjacent structures	Multicystic mass with thick walls or septa and possible curvilinear calcifications	Benign	Matsuoka <i>et al</i> (28)
Cystic lymphangioma	Male gender, pediatric age, asymptomatic or symptoms due to complications, including abdominal pain	Large thin-walled multiseptate cystic mass with attenuation values between fluid and fat	Benign	Konen <i>et al</i> (29)
Cystic neoplasms of the pancreas	See Table II	See Table II	See Table II	See Table II

CT, computed tomography; GISTs, gastrointestinal stromal tumors.

uni- or multi-cystic masses. The malformation appears to arise from sequestration of lymphatic tissue that fails to communicate with lymphatic flow, or from developmental defects during the embryological life stage of the patient, which results from the abnormal budding of the lymphatic endothelium (7,8). However, a pathogenesis associated with abdominal trauma, inflammation due to obstruction of the lymphatic system and radiation

therapy have also been suggested as promoting the secondary development of these tumors (9).

Histologically, lymphangiomas consist of 3 distinguishable variants, capillary, cavernous and cystic; the latter is most common. Cystic lymphangiomas are characterized by cystic spaces and dilated endothelium, containing abundant lymphoid tissue and smooth muscle in the cyst wall, with islands of

Table II. Type and characteristics of pancreatic cystic neoplasms (15).

Type of pancreatic cystic neoplasm	Epidemiological and clinical features ^a	Morphological features on ultrasound and CT scan	Malignant potential
Serous cystadenoma	Female gender, 7th	Microcystic or honeycombed lesion	Rare
Mucinous cystic neoplasm	Female gender, 5th	Macrocytic malignant lesion may have a thickened wall or septations	Degree of epithelial dysplasia
Intraductal papillary mucinous neoplasm	Any gender, 6th-7th	Mixed features of microcystic and macrocytic lesions, and a dilated duct may be present	Degree of epithelial dysplasia
Solid pseudo-papillary neoplasm	Female gender, 4th	Mixed features of a solid mass, fluid and hemorrhage	Rare
Cystic endocrine neoplasia	Any gender, 5th-6th	Variable features	Similar to solid neuroendocrine tumor
Ductal adenocarcinoma with cystic degeneration	Male gender, 6th-7th	Mass with localized adjacent fluid collection	Similar to solid adenocarcinoma
Cystadenocarcinoma in acinar cells	Male gender, 6th-7th	Mixed features of microcystic and macrocytic lesions	Similar to solid type

^a4th, 5th, 6th and 7th indicate the decade of life. CT, computed tomography.

Table III. Type and characteristics of non-neoplastic retroperitoneal cystic lesions.

Lesion	Epidemiological and clinical features	Morphological features on ultrasound and CT scan	First author
Hematoma	History of trauma, ruptured abdominal aortic aneurysm, anticoagulation therapy or blood disease	Radiological features of hematoma	Yang <i>et al</i> (14)
Pancreatic pseudocyst	History of pancreatitis, high amylase or lipase levels, usually in the peripancreatic space	Round or oval fluid collection with a thin or thick wall	Balthazar <i>et al</i> (30)
No pancreatic pseudocyst	Asymptomatic	Unilocular or multilocular fluid-filled mass with thick walls	Ros <i>et al</i> (31)
Lymphocele	History of pelvic or retroperitoneal lymphadenectomy or renal transplantation surgery	Fluid-filled cyst with a low or negative attenuation value due to fat within the fluid	van Sonnenberg <i>et al</i> (32)
Urinoma	History of trauma and presence of moderate or severe hydronephrosis in the majority of patients	Fluid collection and water attenuation that increases progressively following the intravenous administration of contrast material, due to the entry of contrast-enhanced urine in urinoma	Healy <i>et al</i> (33)

CT, computed tomography.

lymphocytes in the lumen (10). Immunohistochemically, cystic lymphangioma endothelial cells express factor VIII-related antigen, CD31 and CD34, which are markers for capillary and lymphatic endothelium (6).

Cystic lymphangiomas are usually asymptomatic and found accidentally. In symptomatic cases, the clinical

presentations are variable depending upon the location and size of the tumor, but are particularly associated with abdominal pain, abdominal distension and the early onset of the feeling of fullness. On occasion, symptoms may be associated with the onset of complications, including intra-cystic bleeding, infection, rupture of the cyst or compression of

adjacent organs, and may present in certain cases as an acute abdomen (3).

A definitive diagnosis of cystic lymphangioma is usually made by histological examination subsequent to surgery or exploratory laparoscopy, and a pre-operative diagnosis is rare. The recommended treatment is radical surgical resection. In case of the involvement of the surrounding tissue, the resection should also include the removal of surrounding tissue to ensure complete excision of the tumor, as incomplete resections may be accompanied by an increased risk of recurrence (50% compared with 7% for complete resection) (11,12).

Conservative methods, including aspiration, cyst enterostomy and peritoneal marsupialization, are now obsolete due to the high rate of recurrence (3).

Following surgical resection, the correct follow-up program for patients remains unclear. In a study conducted by Makni *et al* (12), the cases of 20 patients who underwent surgical resection, followed by physical examinations and abdominal ultrasonography for an average period of 5 months (range, 1-60 months), were evaluated. In total, 2/20 patients (10%) who underwent the surgical removal of the tumor experienced a recurrence of the disease: The first patient relapsed 6 months after a radical intervention and the second patient relapsed 60 months after surgery, due to a partial resection (12). In another previous study, follow-up was considered to be complete at 30 months post-surgery (13).

Despite the absence of large studies in the literature regarding the diagnosis of retroperitoneal cystic masses, distinguishing between neoplastic or non-neoplastic lesions and identifying the type of neoplasm is important, as each tumor demonstrates a varying malignant degeneration risk. A variety of neoplastic retroperitoneal cystic neoplasms (Table I), in particular pancreatic cystic neoplasms (Table II), and non-neoplastic cystic masses (Table III) are considered in the differential diagnosis when a retroperitoneal cystic mass is found (14,15).

In order to diagnose a patient with the aforementioned lesions, certain clinical parameters, including gender, age, presence of symptoms and medical history, particularly a history of pancreatitis, are important to exclude the inflammatory pseudocysts that are associated with chronic pancreatitis (15). The first examination is usually an ultrasound, but assessing the retroperitoneal region is often challenging with this method. By contrast, CT scans allow detailed information on the lesion structure to be obtained through the visualization of the lesion site and size, the presence of calcification or a central scar (highly indicative of serous cystadenomas), the presence of walls, septa and mural nodules, and the involvement of adjacent structures. Particularly in cases of cystic lymphangioma, CT scans show well circumscribed, encapsulated, water-dense, polycystic tumors within septa, which are hardly distinguishable from cystadenomas or from other cystic neoplasms. The attenuation values of CT scans vary between those of fluids and fats. MRI may not provide a better morphological characterization of the mass compared with a CT scan; however, MRI scans reveal the presence of communication between the cyst and pancreatic ducts, which is important in the diagnosis of intraductal papillary mucinous neoplasms (14,15).

The use of endoscopic ultrasound and cyst fluid fine-needle aspiration may be useful to determine the nature and association

of cystic lymphangiomas with other structures, and allows better pre-operative characterization of the lesion. Aspirated fluid may be evaluated from a cytological perspective, including the research of tumor cells and atypical lymphocytes, or from a chemical perspective, including measuring levels of amylase and tumor markers. Carcinoembryonic antigen was indicated to be the most useful marker to differentiate malignant potential-mucinous cysts from serous and non-neoplastic lesions in a large prospective study conducted by Khalid *et al* (16). An increasing level of attention is being focused on the analysis of the DNA quality of fluids and genetic mutation panels, including Kirsten rat sarcoma viral oncogene homolog, p53 and deleted in pancreatic carcinoma 4 mutations, in order to distinguish benign from malignant lesions (16).

Cytological features are useful for the pre-operative diagnosis of lymphangioma, particularly for small and asymptomatic lesions, and include assessment of the triglyceride levels (~5,000 mg/dl; normal level, <3,000 mg/dl) whereby increased triglyceride levels may indicate lymphangioma, and the presence of lymphocytes and milky fluid (17).

The major epidemiological and morphological characteristics of cystic lesions are summarized in Tables I-III. However, determining a pre-operative diagnosis is often challenging, and in the majority of cases, a diagnosis is only possible subsequent to a histological examination of the surgical specimen.

In conclusion, in the presence of a retroperitoneal cystic mass, clarifying whether the mass is a neoplastic lesion is important in order to understand its nature and malignant potential. The retroperitoneal region is a rare localization of cystic lymphangiomas, however, it should be included in the differential diagnosis of cystic lesions (Tables I-III) (18-33). The recommended treatment for retroperitoneal cystic masses is complete surgical excision, as a partial resection is associated with increased rates of recurrence. The follow-up program is not well established. The two patients in the present study underwent a clinical and radiological surveillance program and, at present, are free of recurrence.

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