

A Clinicopathologic and Immunohistochemical Study of Ten Pancreatic Lymphangiomas and a Review of the Literature

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BACKGROUND. Pancreatic lymphangiomas are rare benign tumors, of which only a few cases have been reported in the literature. In this study, the authors present a series of primary pancreatic lymphangiomas.

METHODS. Cases of nonepithelial pancreatic cystic tumors (lymphangiomas) diagnosed between 1966 and 1994 were retrieved from the Endocrine Pathology Registry of the Armed Forces Institute of Pathology. Histologic features (in 10 cases) as well as histochemical and immunohistochemical studies (in 6 cases) were reviewed. Long term patient follow-up data were obtained in 9 cases.

RESULTS. The patients included 8 females and 2 males ages 2–61 years (mean age, 28.9 years) at initial presentation. The tumors were circumscribed and occurred predominantly (in 6 of 10 cases) in the tail of the pancreas. The multicystic, serous, or chylous fluid-filled cystic tumors ranged from 3 to 20 cm (average, 12.7 cm) in greatest dimension. Histologically, the tumors consisted of multilocular cystic spaces of various sizes, lined by endothelial cells. The stroma contained smooth muscle and mature lymphocytes. Immunohistochemistry determined the endothelial lining cells to be factor VIII-R antigen and CD31 positive (in all cases tested) but usually CD34 negative. All patients for whom follow-up data were obtained (n = 9) were alive without evidence of disease an average of 7.2 years after initial diagnosis.

CONCLUSIONS. Pancreatic lymphangiomas occur predominantly in females within a wide age range. Multilocular, fluid-filled cysts, with endothelial immunoreactivity for factor VIII-R antigen and CD31, are characteristic of these tumors. Complete surgical excision of these benign tumors resulted in excellent long term prognoses for all patients studied. *Cancer* 1998;82:2150–8.

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Pancreatic lymphangiomas comprise less than 1% of all lymphangiomas.^{1,2} Many neoplasms and benign conditions of the pancreas can present radiographically and macroscopically as cystic lesions. The cysts may be uni- or multilocular. The cystic nature of the lymphangioma encompasses a broad differential diagnosis, including pseudocysts, microcystic adenomas, mucinous cystic tumors, solid and papillary cystic epithelial neoplasms, cystic adenocarcinomas, ductectatic tumors, pancreatic endocrine neoplasms, duct obstruction, and mesenchymal tumors (e.g., hemangiomas). Mesenchymal tumors of the pancreas account for 1–2% of all pancreatic tumors, with lymphangioma occurring quite infrequently.³

Although there have been a number of single case reports of pancreatic lymphangiomas in the English literature^{1,4–27} since the

TABLE 1
Clinical Presentation

Case no.	Gender/age	Race	Clinical presentation	Tumor size	Location
1	F/31	U	Urinary tract infection, nausea, right upper quadrant pain radiating to the back	19 cm	Adjacent to head
2	F/7	C	Abdominal mass	18 cm	Tail
3	M/2	A	Upper abdominal mass	7 cm	Tail
4	F/32	U	Unknown	8 cm	Tail
5	F/13	C	Right lower quadrant pain, nausea, loss of appetite, dysuria	20 cm	Body
6	F/15	C	Recurrent right upper quadrant pain with nausea, repeated attacks of pancreatitis	15 cm	Head
7	F/59	O	Epigastric pain	>15 cm	Diffuse
8	F/52	C	Incidental finding	7 cm	Tail
9	F/17	C	Left sided abdominal pain, nausea and vomiting	15 cm	Tail
10	F/61	C	Progressive weight loss and pelvic mass on physical examination	3 cm	Tail

C: Caucasian; A = African American; O = Asian; U = unknown.

first description by Koch in 1913,¹⁵ most are clinical or radiologic studies without a pathologic or histologic description. Therefore, we reviewed all cases diagnosed as lymphangiomas of the pancreas from the files of the Armed Forces Institute of Pathology, with an emphasis on the histologic, histochemical, and immunohistochemical findings combined with patient follow-up. This study includes a review of the pertinent literature.

MATERIALS AND METHODS

Ten cases of lymphangiomas of the pancreas were identified in the files of the Endocrine Tumor Registry at the Armed Forces Institute of Pathology between the years 1966 and 1994. These 10 cases were identified in a review of 4810 (0.2%) benign and malignant primary pancreatic tumors (excluding metastatic disease) seen in consultation for the same time period. Hematoxylin and eosin-stained slides, available in all cases, were reviewed. All of the cases met the histologic criteria for lymphangioma as defined by Enzinger: 1) lymphatic spaces lined by endothelium, 2) fascicles of smooth muscle in the septa between the lymphatic spaces, and 3) lymphoid aggregates in the delicate collagenous stroma.²⁸

Periodic acid-Schiff reaction with and without diastase digestion, mucicarmine, and Alcian blue stains were performed, according to standard methods,²⁹ in six cases.

Paraffin blocks and/or unstained slides were available in six cases. Four-micron sections were used for immunophenotypic analysis according to the avidin-biotin method of Hsu et al.³⁰ A commercially available basic antibody panel was applied, which in-

cluded factor VIII-R antigen (Ag) (rabbit polyclonal, 1:800 dilution, Dako, Carpinteria, CA), CD34 (clone QBEnd/10; mouse monoclonal, 1:80 dilution, Biogenex Laboratories, San Ramon, CA), CD31 (mouse monoclonal, 1:40 dilution, Dako), progesterone receptor protein (mouse monoclonal, 1:20 dilution, Novocastra Laboratories Ltd., Newcastle-upon-Tyne, England), type IV collagen (mouse monoclonal, 1:50 dilution, Dako), laminin (mouse monoclonal, 1:8000 dilution, Sigma Immuno Chemicals, St. Louis, MO), a cytokeratin cocktail (AE1/AE3 and CK1), (AE1/AE3, mouse monoclonal, 1:50 dilution, Boehringer Mannheim, Indianapolis, IN, and CK-1, mouse monoclonal, 1:200 dilution, Dako), leukocyte common antigen (CD45 RB, LCA, mouse monoclonal, 1:100 dilution, Dako), smooth muscle actin (mouse monoclonal, clone 1A4, 1:8,000 dilution, Sigma Immuno Chemicals), and HMB-45 (mouse monoclonal, 1:100 dilution, Dako). Factor VIII-R Ag, CD34, cytokeratin, and type IV collagen required predigestion for 3 minutes with 0.05% Protease VIII (Sigma Chemical Co., St. Louis, MO) in a 0.1 M phosphate buffer, pH 7.8, at 37°C. Standard positive controls were used throughout. Negative controls were performed on each case with serum.

RESULTS

Clinical

The patients included 8 females and 2 males, ages 2–61 years, with a mean age at initial presentation of 28.9 years. The patients' initial presenting symptoms included nausea, pain, and abdominal mass, usually in the left lower quadrant. Vomiting was reported by 1 patient. There were no specific or significant labora-

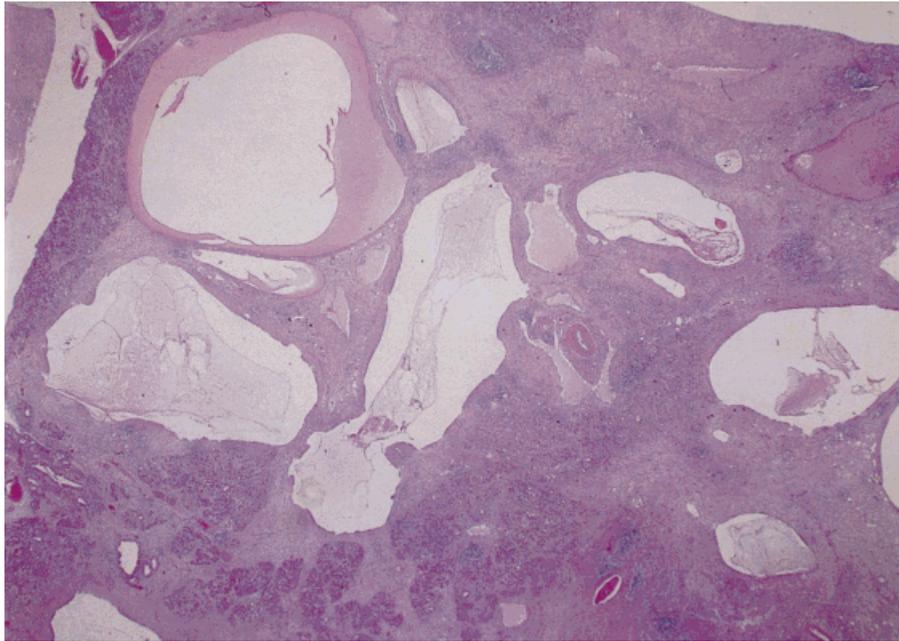


FIGURE 1. Lymphatic channels of various sizes within the pancreatic parenchyma are shown. Note the lymphoid aggregates around the lymphatic channels.

tory abnormalities. Table 1 summarizes the clinical data.

All 10 patients were treated surgically by partial pancreatectomy or distal pancreatectomy and cystectomy (1 patient was initially treated with partial cystectomy, and complete excision followed within a short time). External drainage was performed initially on one patient, followed by a partial pancreatectomy. Follow-up was obtained in nine cases, with one patient lost to follow-up. All of the patients were alive without evidence of disease or recurrence, without additional therapy, 3–11 years after initial presentation, with an average follow-up of 7.2 years.

Pathology

Six of the patients had a tumor in the tail of the pancreas, two patients had a tumor in the head, one patient had a tumor in the body, and one patient's lymphangioma involved the whole pancreas diffusely. The tumors ranged in size from 3 to 20 cm in diameter, with an average size of 12.7 cm. All of the tumors were multicystic, with cysts of various sizes ranging from microscopic to as large as 10 cm. The macroscopically identifiable cysts had pinkish-gray walls with a smooth inner lining. Focal hemorrhage was identified. The cysts contained either straw-colored or chylous fluid.

Histologically, the cystic channels were lined by flattened-to-slightly-raised endothelial cells found intimately intermingled with the pancreatic paren-

chyma (n = 4) (Fig. 1) or abutting the pancreatic tissue (n = 6). The walls of these channels contained a significant amount of collagen and irregularly distributed fascicles of smooth muscle (Figs. 2A and 2B). Mature lymphocytes were present within the lumen of the lymphatic channels as well as in the cyst walls. Compression of the surrounding pancreatic parenchyma by the lymphangioma resulted in pancreatic atrophy (n = 6).

Histochemistry and Immunohistochemistry

The endothelial lining cells did not react with periodic acid–Schiff stain (with or without diastase pretreatment), mucicarmine, or Alcian blue, nor did they react with anti-cytokeratin, confirming a lack of epithelial differentiation (Fig. 3). The endothelial cells lining the cystic spaces were strongly and diffusely positive in all cases for factor VIII-R Ag and CD31 (Fig. 4). CD34 was negative in five cases, but there was focal, weak reactivity in one case (Fig. 4). Basement membrane was detected in all cases tested (n = 6), with either type IV collagen or laminin immunoreactants, identified by a focal granular reaction. This finding suggested that there was no linear basal membrane present. Smooth muscle actin accentuated the irregular bundles of smooth muscle within the septa. Progesterone receptor immunoreactivity was not identified in the endothelial cells or within the stromal cells. A positive LCA (CD45-RB) reaction confirmed the identity of mature

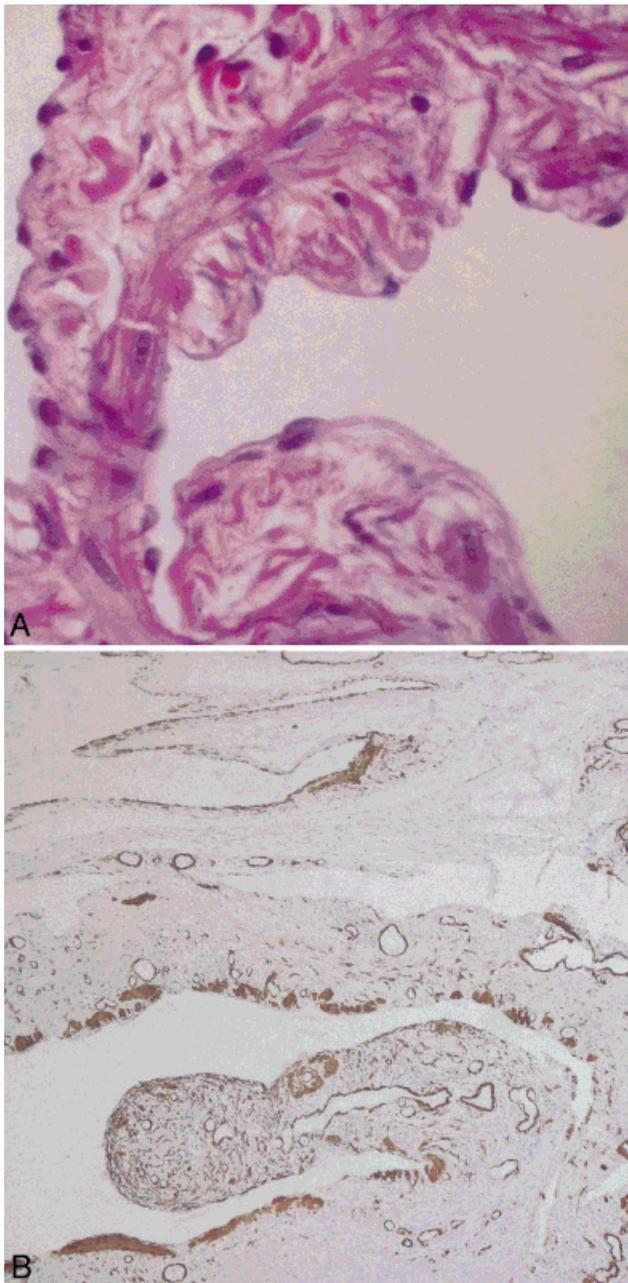


FIGURE 2. (A) Irregular smooth muscle bands in the lymphatic walls are shown. Endothelial cells can be identified within the lymphatic lumina. (B) Irregular smooth muscle elements of the vascular channel walls are shown with anti-smooth muscle actin.

lymphocytes. HMB-45 was negative in all cases (Table 2).

DISCUSSION

Lymphangiomas are slow-growing tumors that are generally considered to be of pancreatic origin if they are within the parenchyma, adjacent to the pancreas,

or connected to the organ by a pedicle.¹⁸ When lymphangiomas occur in the retroperitoneum, they only rarely project into the abdominal cavity proper.^{7,11,31,32} Lymphangiomas can originate in any organ (except for the eye and neural tissue⁴), although more than 95% occur in the soft tissues of the head and neck (cystic hygroma) and axilla, with less than 5% occurring in the abdominal cavity.³³ Approximately 5% of the abdominal cavity lymphangiomas are retroperitoneal in location, usually in the lumbar region.^{28,31,33} Pancreatic lymphangiomas make up a very small percentage of this already small group of tumors.

The macroscopic findings of our lymphangioma cases match the macroscopic findings (of a solitary, multicystic mass) presented in the literature.³⁴ The cysts may connect with each other, as a number of our cases did, suggesting that they are dilated lymphatic channels.^{14,15,35} These channels contain serous, serosanguinous, or chylous fluid. The lining of the cysts is smooth, with thin cyst walls. The lesions are usually solitary; however, occasional cases have been reported to occur in the setting of multiple lymphangiomas, i.e., lymphangiomatosis.⁵

The microscopic appearance of lymphangiomas consists of dilated and/or interconnecting vascular channels (cysts) of varying size separated by thin septa. The cystic spaces are lined by flattened-to-slightly-elevated endothelial cells. The cyst walls contain various amount of collagenous connective tissue, irregular smooth muscle fascicles, occasional adipocytes, and mature lymphocytes.^{28,36} The smooth muscle found in the wall, in combination with the lymphocytes (both in the wall and in the vascular lumina), is most suggestive of the diagnosis. Phlebolith-like structures can be seen,^{6,12} although we did not see any in our cases. The surrounding pancreatic parenchyma is often atrophic with focal fibrosis. The diagnosis can be suggested by percutaneous fine-needle aspiration biopsy,^{21,24} but it should be confirmed with surgical excision.

The diagnosis of pancreatic lymphangioma is supported immunohistochemically. Our findings confirm those of others.³⁷⁻³⁹ Factor VIII-R Ag and CD31 are sensitive, specific, and reliable markers for the identification of lymphatic endothelium. Although focal, weak CD34 (QBEnd/10) endothelial cell reactivity was noted in one of our cases, the remaining five cases did not demonstrate any such reaction, suggesting that a battery of all three markers (FVIII-R Ag, CD31, and CD34) may be useful in discriminating between vascular and lymphatic endothelium.

It has been suggested by several authors^{17,28} that endothelial cells do not produce a continuous basal membrane and that pericytic cells are not detected.

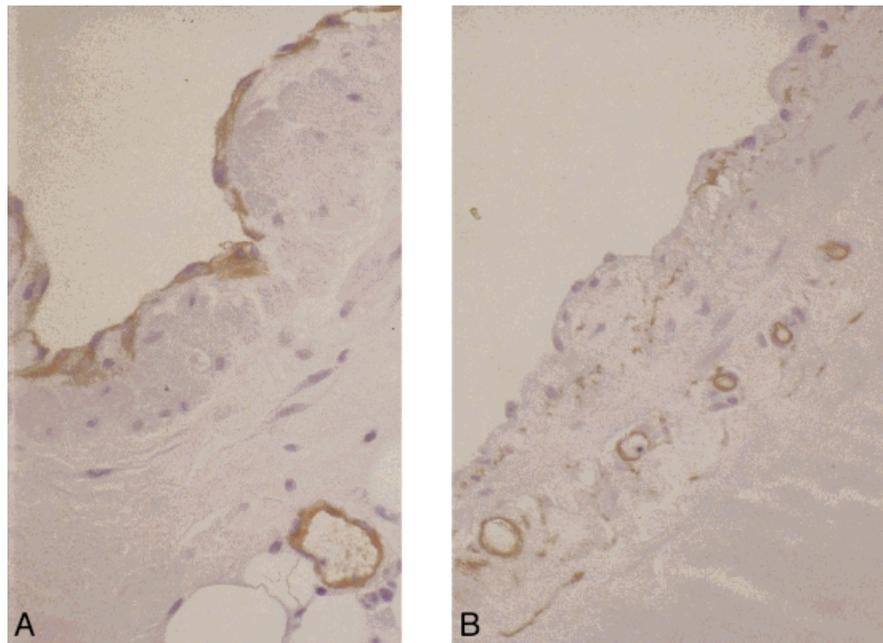


FIGURE 3. The endothelial lining expresses no epithelial markers (cytokeratin, B), but shows a positive immunoreaction with factor VIII R antigen (A).

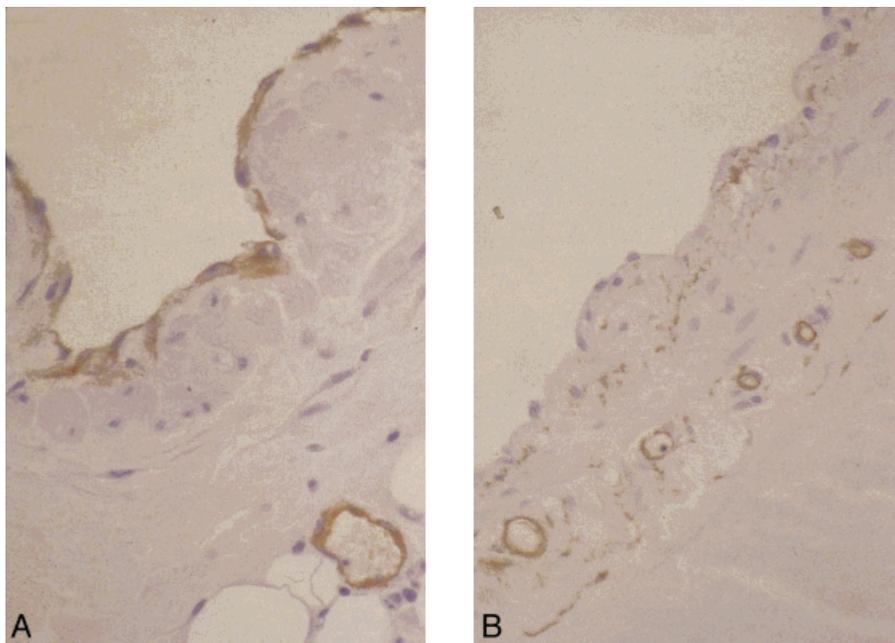


FIGURE 4. The lymphatic endothelium is immunoreactive with factor VIII R antigen (A), in contrast to the negative immunoreactivity with CD34 (B).

The detection of basal membrane fragments with type IV collagen and laminin immunohistochemical reactions in our cases confirmed this conclusion.

Of the three histologic variants of lymphangiomas described (capillary, cavernous, and cystic), the capillary type has not, to our knowledge, been reported to occur in the retroperitoneum.⁴⁰ The differences between the cavernous and cystic lymphangiomas seem

to be more quantitative than qualitative. A firmer surrounding parenchymal tissue may play a role in the degree of cyst formation.^{18,28,34,41}

Several cystic lesions of the pancreas must be considered in the differential diagnosis (Table 3). Inflammatory lesions, including pseudocyst (usually unilocular), generally have characteristic clinical, radiographic, and laboratory findings distinctive from

TABLE 2
Immunohistochemical Reactions

Case no.	Keratin	Factor VIII R-Ag	CD31	CD34	SMA	Collagen IV	Laminin	Progesterone receptor	HMB-45
1	-	+	+	-	+	-	+/F	-	-
3	-	+	+	-	+	n/a	+/F	-	-
5	-	+	+	-	+	+/F	+/F	-	-
6	-	+	n/a	-	+	+/F	+/F	-	-
7	-	+	+	+/F	+	+/F	+/F	-	-
8	-	+	+	-	+	+/F	+/F	-	-

SMA: smooth muscle actin; -: negative; +: positive; n/a: not applicable; F: focal.

TABLE 3
Differential Diagnosis

Type of lesion	Classification
Nonneoplastic	a) Inflammatory
	Pseudocyst
	Ductal ectasia in chronic fibrosing pancreatitis
	b) Infectious
	<i>Echinococcus</i> cyst
c) Inherited	Polycystic pancreas associated with polycystic kidneys
	Cystic fibrosis
	Renal, pancreatic, and hepatic dysplasia sequence
	von Hippel-Lindau syndrome
	Neoplastic
Microcystic adenoma	
Teratoma	
Hemangioma	
Lymphangioma	
Lymphangiomyoma	
b) Malignant	
Cystadenocarcinoma	
Mucinous cystic neoplasm of low grade malignant potential	
Intraductal papillary mucinous neoplasm	
Cystic degeneration in other malignant tumors	

lymphangioma. The epidemiologic setting, a positive serology and peripheral eosinophilia, are important in the accurate preoperative diagnosis of an echinococcal cyst.⁴² On histology, echinococcal cysts lack an epithelial lining and contain a laminated gelatinous membrane, daughter cysts, and/or scolices and hooklets. Cysts in the pancreas that are features of polycystic renal disease are epithelial in nature, but the pancreatic cysts are not the only clinical presentation of this disease; the renal symptoms generally overshadow the pancreatic findings. In von Hippel-Lindau syndrome, various epithelial, cystic pancreatic lesions may occur, including simple cysts, microcystic (serous) adenoma, and cystic islet cell tumors, confirmed with keratin immunoreactivity.⁴³⁻⁴⁵

Neoplastic epithelium-lined cysts (benign or malignant) need to be separated from lymphangioma by

TABLE 4
Literature Review

Patient characteristics	Literature ^a	Current study	Aggregate results
Female:Male	25:16	8:2	33:18
Tumor location			
Head	18	2	20
Body	18	2	20
Tail	16	5	21

^aReferences 1 and 4-27 were reviewed.

histologic examination, as the clinical presentation and radiographic appearance may be similar.^{16,21,46} Although the epithelial nature of the tumors is usually apparent on hematoxylin and eosin-stained slides, positive histochemical reactions with mucicarmin, periodic acid-Schiff reaction, and/or Alcian blue combined with immunoreactivity for epithelial markers (keratin, CAM5.2, B72.3, carcinoembryonic antigen, DuPan-2, and CA19-9) can confirm the diagnosis. Almost all neoplasms of the pancreas may undergo cystic degeneration;⁴⁷ therefore, careful histologic examination is necessary to exclude other diagnostic possibilities.

Hemorrhage within a lymphangioma may raise the possibility of a hemangioma. These neoplasms are even more rare than lymphangiomas, occurring in a similar age distribution.^{4,17,31,48} The distinction can be made by performing a battery of immunohistochemical reactions, including factor VIII-R Ag, CD31, and CD34. Lymphangiomyomas should also be considered in the differential diagnosis; however, those tumors occur predominantly in the lungs and show a significant smooth muscle proliferation, and the proliferating smooth muscle cells are HMB-45 positive.⁴⁹ None of our cases reacted with HMB-45, nor was there significant hemorrhage.

The literature reports a wide age spectrum for patients at initial presentation, and our mean age at presentation (25.3 years) supports the conclusions of a

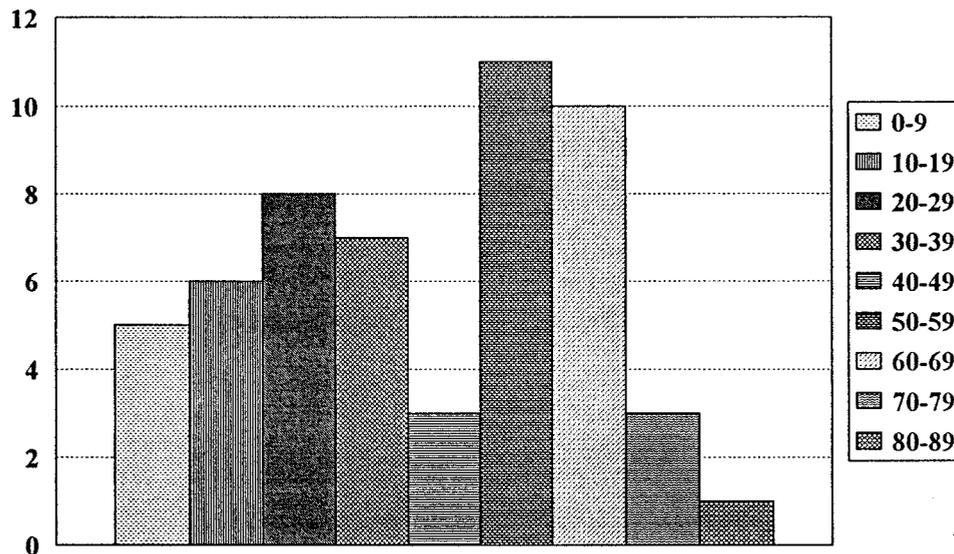


FIGURE 5. Age distribution is shown for current cases combined with cases reported in the literature.^{1,4-27}

few authors who reported a young age at presentation for patients with intra-abdominal and retroperitoneal lymphangiomas^{27,33,50,51} (Table 4). However, when our cases and those reported in the literature are combined, there is equal presentation among all age groups. While the female-to-male ratio is 25:16 in the literature^{1,4-27} and 8:2 in our series, the combined ratio is approximately 2:1. Therefore, there does seem to be a true predilection for females. In our series, slightly more cases involved the tail of the pancreas ($n = 6$); but when our results are combined with those reported in the literature, all regions of the pancreas seem to be affected equally (Fig. 5). In conclusion, a combination of our results with those of a literature review of primary lymphangiomas would indicate a female predominance at any age and in any location within the pancreas.

The clinical presentation is nonspecific, including vague abdominal pain, nausea, vomiting, and a palpable mass. As the symptoms may be related to the compression of neighboring organs,^{11,26,52} it is unusual, based on clinical findings, to suggest a correct diagnosis preoperatively. Occasionally patients present with acute abdominal symptoms that are perhaps related to a torsion of the pedicle, rupture, or hemorrhage into the lymphangioma.^{34,53} A number of patients reported in the literature were asymptomatic with an incidental diagnosis of lymphangioma^{14,26,40,48} found on physical examination or radiographic studies for unrelated diseases.

Radiographic imaging of the abdomen, and specifically the pancreas, assists in the preoperative evaluation by defining the exact anatomic location and the

content of the cyst. Ultrasound or computed tomography examinations are useful because they reveal septated masses filled with fluid.^{16,24,51} Magnetic resonance imaging plays a complementary role in these cases by suggesting the content of the cysts.^{5,14,25,40} Endoscopic retrograde cholangiopancreatography may be a valuable, though less direct, method for evaluating these lesions.⁵⁴

The histogenesis of the tumor is uncertain. Proposed theories have suggested an inherited abnormality, an embryologic origin, a traumatic origin, or a true neoplasm.^{31,35,55-59} Our findings, especially in light of the young age of patients at initial presentation, may support the notion of a congenital malformation, but there are insufficient data to draw a conclusion. Oral contraceptives, hyperprogesteronemia, and pregnancy seem to promote the growth of lymphangiomas,⁵⁶ perhaps explaining partially the female predominance of pancreatic lymphangiomas. However, we did not document progesterone receptor immunoreactivity of the endothelial cells or of the stroma.

In conclusion, pancreatic lymphangiomas are rare neoplasms that generally occur in young female patients with vague abdominal symptoms. Lymphangiomas are multicystic tumors both radiographically and macroscopically. Histologically, the cysts are lined by benign-appearing endothelial cells that react with anti-CD31 and anti-factor VIII-R Ag antibodies. As the clinical and radiographic appearance of lymphangiomas overlap the findings for other pancreatic tumors (e.g., mucinous cystic neoplasms, cystadenomas, and teratomas), exploratory laparotomy with complete surgical excision (rather than marsupialization) would

be the treatment of choice.^{1,2,4,7,13,33,34,36,46,48,50,53} All patients in our series and all patients in the literature were alive without evidence of disease at last follow-up, with only a single recurrence or perhaps the development of a new primary reported as part of lymphangiomatosis.⁵

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