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A Pathologic Study of Abdominal Lymphangiomas

Abdominal lymphangiomas are uncommon angiomatous tumor occurring mainly in childhood. This is a retrospective clinicopathologic study of 17 cases of abdominal lymphangioma. The patients included are five children and 12 adults, with a mean age at initial presentation of 30.7 years (age ranges 3-63). The locations of the tumors were mesentery (5), retroperitoneum (4), colon (3), omentum (3), mesocolon (1) and gallbladder (1). Infiltrative growth was more common pattern than entirely circumscribed pattern. Masses were mostly multilocular cysts and contained chyle or serous fluid. On immunohistochemical staining, 16 cases were reactive for either CD31 or factor VIII-related antigen. These fact would suggest that intra-abdominal lymphangiomas simulate the immunohistochemical features of collecting lymphatics. Follow up was possible in 12 cases for 3-50 months (mean 19 months) and only one patient showed local recurrence. Although abdominal lymphangiomas are rare in adulthood and correct preoperative diagnosis is difficult, awareness of such a possibility in adulthood will contribute to make a correct preoperative diagnosis.

Key Words: *Abdominal neoplasms; Lymphangioma; Adult; Immunohistochemistry*

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INTRODUCTION

Lymphangiomas usually occur in the head and neck portions or axillary areas during childhood, suggesting a congenital etiology (1, 2). Intra-abdominal lymphangiomas are rare and comprise less than 5% of all lymphangiomas (3-9). Although about 60% are present in patients under the age of five years, significant numbers of abdominal lymphangiomas do not manifest until adulthood (8). These facts attribute to the difficulty of diagnosing lymphangioma at preoperative stage especially in adult patients, thus in most instances, diagnosis was made at the time of operation or after histologic examinations (3). Histologically, diagnosis of lymphangioma is not so difficult, but peritoneal cystic mesothelioma should be excluded in adult patients. In addition, lymphangioma should be differentiated from hemangioma in case of secondary hemorrahge being present. Although there have been a number of single case reports (5, 6, 10-13) and some clinicopathologic studies of abdominal lymphangiomas (3, 4, 7), most of them described pediatric cases. Furthermore, there have been some controversial reports about the immunohistochemical characteristics of lymphatic endothelium in lymphangioma (12-16). Here, we reported our experience of 17 abdominal lymphangiomas, including 12 adulthood cases, with emphasis on histopathologic and immunohistochemical findings.

MATERIALS AND METHODS

All patients who had undergone operation for intra-abdominal and retroperitoneal lymphangiomas at Seoul National University Hospital, Seoul National University Children's Hospital and Samsung Seoul Hospital, Seoul, Korea, between 1989 and 1997, were reviewed. Hematoxylin and eosin-stained slides were available in all cases and reviewed. Among them, 17 cases which fulfilled more than four of the following five standard histologic criteria were selected: 1) the cysts were lined by flat endothelium rather than cuboidal or columnar epithelium; 2) small lymphatic spaces were present in the cyst wall; 3) lymphoid aggregates were present in the cyst wall; 4) foam cells containing lipoid material were present in varying numbers; and 5) smooth muscle was present in the cyst wall (3). All the specimens were formalin-fixed and paraffin-

embedded, and 4 μm sections were cut for immunohistochemical studies. For immunohistochemistry, the avidin-biotin-peroxidase complex method was used, employing antibodies against factor VIII-related antigen (polyclonal, 1:100, DAKO, Capenteria, CA, U.S.A.), CD31 (Clone JC70A, monoclonal, 1:30, DAKO) and cytokeratin (Clone MNF116, monoclonal, 1:50, DAKO). Sections to be stained for cytokeratin were trypsinized for 10 min. The monoclonal antibody MNF116 reacts with an epitope which is present in a wide range of cytokeratins. Appropriate positive and negative controls were used for all the antibodies.

RESULTS

Clinical findings

Age of the patients ranged from three to 63 years (mean 30.7) at the time of initial presentation and the patients included 10 males and seven females. There were five cases of children and 12 cases of adult patients. Characteristic clinical and pathologic findings of the 17 cases are summarized in Table 1. All the patients were symptomatic with abdominal pain, palpable mass, vomiting, or gastrointestinal hemorrhage. Clinical signs and symptoms varied and were not specific. A majority of patients complained of abdominal pain that was usually crampy in nature, intermittent, and characterized by subacute to acute onset. Rectal bleeding was also found. Mean duration of symptoms was 20.3 months. Interval from onset of symptoms to operation ranged from one month to 62 months. One lesion was found incidentally during the operation for colon cancer (case 9). Five cases occurred in the mesentery, four in the retroperitoneum, three in omentum and colon, respectively, and one in mesocolon and gallbladder, respectively.

While all five pediatric cases were diagnosed preoperatively as lymphangioma (case 13, 17) or mesenteric cyst (case 14-16), none of the adult patients was diagnosed preoperatively as lymphangioma. Various diagnoses were assumed for adult patients, which attributed to the some difficulties of patient management (Table 1).

Ten patients were treated with wide excision or radical surgery, six with simple excision, and one with incomplete excision followed by radiotherapy (case 5). In case 5, the tumor showed diffuse infiltrative growth along the lymphatics, so that a complete excision was impossible. During follow up, the patient showed a locally recurrent mass in the same area.

Pathologic findings

Eight of 17 cases were classified as cystic lymphangiomas made up of grossly visible interconnecting cysts. The remaining nine cases were cavernous lymphangiomas which were sponge-like compressible lesions composed of microscopic cysts. As many tumors showed combined features of both types, classification was based on the predominant features. Capillary type was absent. Most

Table 1. Clinical and pathological features of 17 patients

Case	Age (yr)	Sex	Location	Size (cm)	Initial Diagnosis	Follow-up (months)	Operation	Type	Border	Factor VIII related Ag	CD31
1	22	M	Mesentery	10×8	Obstruction	20	Wide excision	Cavernous	Poor	+	+
2	53	F	Cecum	3×2.5	Polyp	14	Right hemicolectomy	Cavernous	Poor	±	+
3	36	M	Gallbladder	8.5×7.5	Cystadenoma	8	Cholecystectomy	Cystic	Good	+	+
4	64	F	Retroperitoneum	7×6	Liposarcoma	4	Simple excision	Cystic	Poor	+	+
5	62	M	Retroperitoneum	Unmeasurable	Lymphoma	17	Incomplete removal with radiotherapy	Cavernous	Poor	+	+
6	31	F	Retroperitoneum	4×3	Hemangioma	50	Simple excision	Cavernous	Poor	+	±
7	36	M	Mesentery	8×3	Cyst	Loss	Wide excision	Cystic	Good	+	+
8	48	M	Ascending colon	3×3	Cancer	Loss	Right hemicolectomy	Cavernous	Good	-	-
9	56	M	T. colon	2×2	Polyp	23	Left hemicolectomy	Cavernous	Good	±	+
10	19	M	Mesentery	20×18	Lymphoma	20	Whipple's operation	Cavernous	Poor	+	+
11	42	M	Retroperitoneum	9.5×6	Pseudocyst	20	Wide excision	Cystic	Good	+	+
12	28	F	Mesentery	14×10	Ovary cancer	6	Wide excision	Cavernous	Poor	+	+
13	4	M	Mesentery	20×8	Lymphangioma	3	Wide excision	Cystic	Poor	+	+
14	3	F	Omentum	30×20	Cyst	Loss	Simple excision	Cystic	Good	+	+
15	4	F	Omentum	25×25	Cyst	Loss	Simple excision	Cystic	Good	+	+
16	6	F	Omentum	6×5	Cyst	24	Simple excision	Cystic	Good	+	+
17	8	M	Mesocolon	10×7	Lymphangioma	Loss	Wide excision	Cavernous	Poor	+	+

Ag, antigen; T, transverse; Loss, lost to follow-up

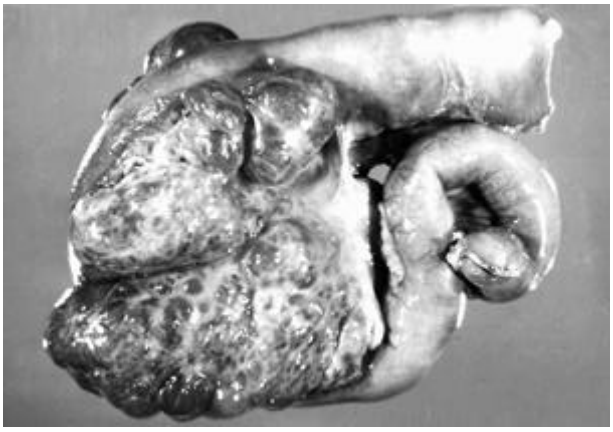

Fig. 1. Gross surgical specimen of large multicystic lymphangioma involving both small bowel and mesentery (case 12).

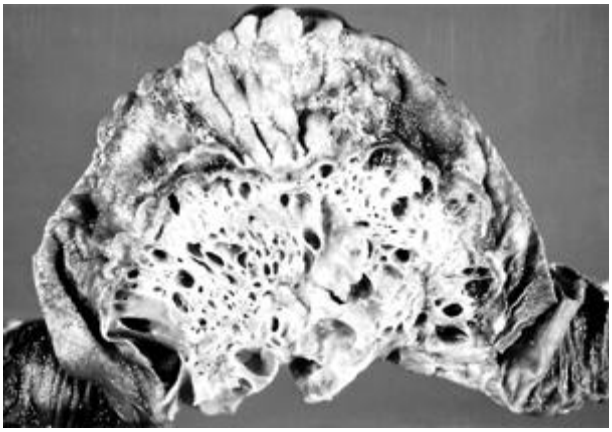

Fig. 2. Cut section of the lesion reveals many dilated cysts and sponge-like features.

lesions were solitary and multilocular cystic masses or sponge-like compressible lesions. They measured from 2 to 30 cm in the largest diameter and the diameters were over than 5 cm in 12 cases. The masses with infiltrative borders were more common than entirely circumscribed masses.

In cases arising from mesentery and omentum, lesions were larger than the rest of the cases. In case 12, the specimen was a U-shaped loop of the small bowel, approximately 55 cm in length (Fig. 1). In the mesenteric attachment, there were numerous cystic structures of varying sizes. These cysts involved a whole layer of small bowel wall as well as extensive area of the mesentery. The mass showed an infiltrative border. A wide resection was performed. The mucosal layer exhibited numerous yellowish speckles with exudate. Some areas of the lesion had thick walls, which were more or less solid, and cut surface showed a honey-combed or spongy appearance (Fig. 2). The other cases arising in the mesentery (case 1, 7, 10, 13) showed almost the same features. Microscopically, the cystic spaces were lined by flattened endothelial cells in all cases. In case 10, sections of the mesentery and jejunum revealed numerous cystic structures and cavernous spaces, some of which were filled with eosinophilic proteinaceous fluid (Fig. 3). The cystic walls were often composed of connective tissue consisting of edematous fibrous tissue, lymphoid cells and smooth muscle fibers. Mucosal glands were widely separated by the cysts and were actually flattened on the surface. These cystic structures were also seen in the muscularis propria, but they were not as prominent as in the submucosa and serosa. There were extensive acute inflammation and hemorrhage in one portion of the adjacent bowel wall and within the cysts. In case 1, there were numerous nerve bundles incorporated within the lymphangiomatous walls, and some protruded into the lumen. These findings were peculiar in comparison with other instances.

Three pediatric patients had cystic lymphangiomas in the omentum (case 14- 16). They were composed of variously-sized cysts ranging from 1 mm to 12 cm in diameter, often communicating each other, and lined with endothelium.

In case 3, the specimen was a cholecystectomized gallbladder, showing multicystic change (Fig. 4). In the operative field, the mass was limited to the gallbladder and had no apparent communication with the biliary tract. Grossly, the cysts varied in size and serous fluid filled the cyst. The wall of the cysts was reddish yellow. On histologic examination, the cysts were also lined by flattened endothelium and filled with pinkish proteinaceous material.

Three patients (case 2, 8, 9) had polypoid cavernous lymphangiomas in the colonic wall and they received a right hemicolectomy (case 2, 8). The other patient, who

Fig. 3. Microscopic feature of lymphangioma. Large endothelial-lined cystic spaces in the mucosa, submucosa and muscularis propria are present (H&E, ×40).

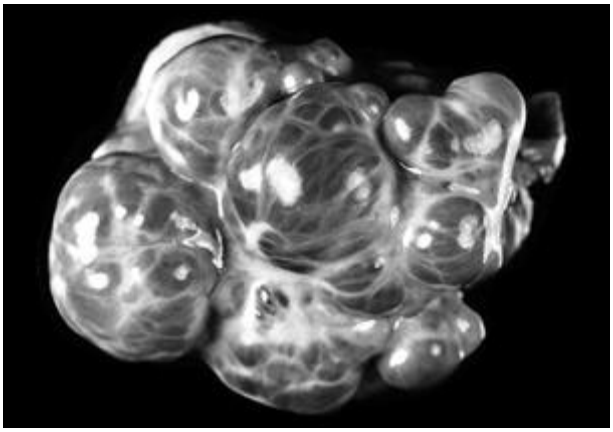

Fig. 4. Cystic lymphangioma of gallbladder. Entire gallbladder is replaced by multicystic lesions which are filled with translucent fluid.

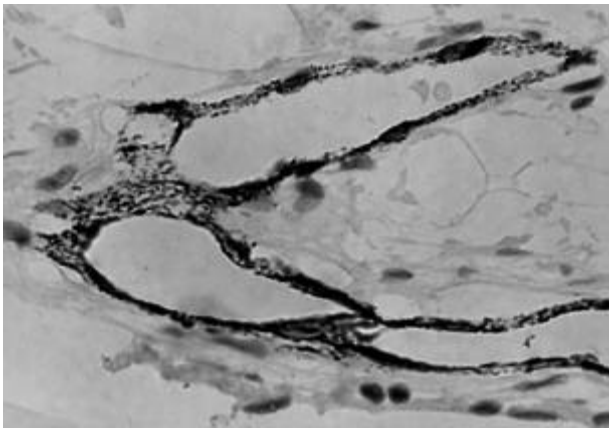

Fig. 5. Immunohistochemical staining for factor VIII-related antigen. The flat endothelial cells lining lymphatics show granular positive reaction in the cytoplasm (×200).

was associated with sigmoid colon cancer, received left hemicolectomy (case 9). The lesions were polypoid lesion into the lumen and appeared soft, easily deformed, grayish pink, fluid filled masses with small lobulations. Histologic examination revealed characteristic features of lymphangioma. Cystically dilated spaces lined by endothelium and separated by fibrous septa were present in the submucosa (case 8, 9) or whole layer (case 2). In case 2 and 8, lymphoid follicles with germinal center formations in the stroma between the lymphatic spaces were noted.

Immunohistochemistry

All the cases were available for immunohistochemical examinations. In 16 cases, flattened endothelial cells lining the cystic spaces showed positive reaction for either factor VIII-related antigen or CD31. The immunoreactive products were weaker than those of venous endothelial cells. Fourteen of the 17 cases showed immunoreactivity for the factor VIII-related antigen (Fig. 5). CD31 was positive in 15 of the 17 cases. In all the cases showing positive reaction with the two antibodies, the endothelial cells lining lymphatic spaces exhibited focal positive reaction. In case 8, the endothelial cells lining the lymphatics were not reactive for the two antibodies. None of the lymphangiomas showed any reactivity for cytokeratin.

DISCUSSION

Abdominal lymphangiomas are rare benign angiomatous tumor, being less than 5% of all lymphangiomas (8, 9). Although lymphangiomas usually manifest during childhood, abdominal lymphangiomas could not be detected until adulthood (8). As most of the reported cases have described pediatric patients, the lesions occurring in adult might cause some difficulties in the management of patients preoperatively and evaluation of adequate range of operative resection. In our series, a preoperative diagnosis of abdominal lymphangioma was seldom made in the adult case. In case 2 and 8, the patients underwent right hemicolectomy on the suspicion of cancer and polyp, which could have been prevented if exact diagnosis was made preoperatively. On the contrary, clinician could suspect abdominal lymphangiomas (case 13, 17) or mesenteric cysts (case 14-16) in the pediatric cases. These facts would be mainly due to the unawareness of adulthood lymphangioma. With a combination of radiological studies, especially ultrasonography, the diagnosis could usually be made in pediatric cases (17). Therefore, awareness of such a possibility in adulthood abdominal tumors will contribute to correct preoperative diagnosis and prevent unnecessary treatment or undertreatment.

It is important to distinguish intra-abdominal lymphangioma from cystic form of peritoneal mesothelioma. Lymphangioma is characterized by stromal aggregates of lymphocytes, an endothelial lining that usually stains positively with factor VIII-related antigen or CD31, and that is often surrounded by a layer of smooth muscle tissue. The tumor cells of mesothelioma stain positively for cytokeratin and epithelial membrane antigen, a distinguishing feature from lymphangioma (18). In case 8, although the endothelial cells of lymphatic spaces did not show any positive reactivity with factor-VIII related antigen and CD31, the presence of following features would support the diagnosis of lymphangioma: 1) many lymphoid aggregates in the cystic wall, 2) flat endothelial lining

of cystic spaces rather than cuboidal epithelium, 3) eosinophilic proteinaceous material in the cystic spaces, and 4) smooth muscle in the cystic wall. In addition to these histologic features, the lining cells did not react with cytokeratin immunostaining. Lymphangioma should be differentiated from hemangioma in case of secondary hemorrhage being present. Histologically the presence of lymphoid aggregates in the stroma and more irregular lumina with widely spaced nuclei favor the diagnosis of lymphangioma over hemangioma (8). It has been known that the immunohistochemical procedures for endothelial markers are not helpful for differentiation from each other.

Of the three histologic variants of lymphangiomas described, the capillary type was absent in our series and has not been reported to occur in the abdomen and retroperitoneum (14). Cavernous type was most frequently found in the mesentery region and colonic wall. However, the classification is often arbitrary due to frequent combining features in one lesion (8). Here, we included a rare case of cystic lymphangioma of the gallbladder (case 3). The cystic nature and its location encompassed various differential diagnoses at preoperative stage, including mucinous cystic tumors, ecchinococcal cyst of liver and hemangioma. To our best knowledge, only one case of lymphangioma involving gallbladder has been reported in the literature (11).

There was no constant clinical pattern of lymphangiomas, sometimes the symptoms were those of a cystic abdominal mass and at other times the symptoms arose from complications. An acute abdominal pain might be caused by torsion of the cysts, by volvulus of the involved portion of bowel and mesentery, or by secondary inflammation. Another peculiar feature was the presence of abundant peripheral nerve bundles in case 1, whose complaint was severe cramping pain. This case was already reported as the relation of the pain mechanism to abundant nerve trunks incorporated within the cystic wall (10). None of the other cases showed such abundant nerve bundles in the cystic wall.

There are several numbers of monoclonal antibodies to identify endothelial cells, such as factor VIII-related antigen (19), CD31, CD34 (20) and Ulex lectin (21). Although Ulex lectin is more sensitive than factor VIII-associated antigen in recognizing normal endothelium (21), its binding is less specific for endothelium and it also recognizes antigens in various types of epithelium (22). In this study, factor VIII-related antigen and CD31 were used for the detection of endothelial cells of lymphangiomas. In most of the cases, endothelial cells lining lymphatic spaces reacted with both endothelial markers. There has been controversial reports about immunohistochemical characteristics of normal lymphatic endothelium and lymphangiomas. Some authors described the negative immunoreaction for factor VIII-related antigen of the lymphatic endothelium in the lymphangioma which arise from breast and abdominal wall (12, 13). On the contrary, others reported positive reaction for endothelial markers of the lymphatic endothelium (15, 16). Most pathologists used factor VIII-related antigen to distinguish capillary blood vessel from lymphatic vessel. However, Werner (1995) described that the endothelium of collecting lymphatics contained high concentrations of factor VIII-related antigen, while it was found only in small amounts or not at all in the endothelium of initial lymphatics (15). In our series, most cases showed positivity for factor VIII-related antigen, which simulated the features of the endothelium of collecting lymphatics. These fact would suggest that intra-abdominal lymphangiomas probably arise from collecting lymphatics rather than initial lymphatics.

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