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Original Article

Vascular malformations and hemangiolymphangiomas of the gastrointestinal tract: morphological features and clinical impact

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Abstract: Purpose: The purpose of our study was to describe the morphological features of gastrointestinal vascular malformations (VM) and of hemangiolymphangiomas (HLA) and to establish correlations with clinical characteristics. Significant findings: Fifteen VMs and 12 HLAs that were encountered over a period of 22 years, were retrospectively analyzed. The VMs often involved the colon, small intestine, but also the stomach, whereas none of the HLAs arose in the stomach. VMs were more frequently associated with gastrointestinal bleeding, ulcer and were larger than HLAs ($p<0.01$ for all comparisons). Intralesional hemorrhage and thrombosis were associated with VM ($p=0.02$ and $p=0.05$). Surgical resection was performed for 1 HLA and 14 VMs. Vessel abnormalities such as shunt vessels, wall tufts (excrescences) and arterialized veins were more frequent in VMs ($p=0.01$, $p=0.04$ and <0.01, respectively) whereas aneurysm-like cavities were observed in both lesion types. Mucosal abnormal vessels were observed only in VMs, whereas HLAs were associated with mucosal lymphatic clusters ($p<0.01$). Most HLAs contained a D2-40 heterogeneously positive lymphatic component, were Glut-1 negative and CD31 reactive. There was no statistical difference in occurrence of associated autoimmune, tumoral and cardiovascular conditions between the two patient groups. Conclusions: The results of our study suggest that morphological features such as increased size, ulcer, thrombosis, hemorrhage and presence of aberrant mucosal vessels favor the diagnosis of VM. Co-existence of other clinical conditions such as cardiovascular disease, encountered in association with both lesion types, might exacerbate a tendency towards hemorrhage.

Keywords: Vascular malformation, hemangiolymphangioma, gastrointestinal tract, histology, immunohistochemistry

Introduction

Benign vascular lesions or tumors are rare in the gastrointestinal tract.[1-4] Other than for angiomas (hemangiomas and lymphangiomas), the terms used, including arteriovenous malformation, venous or vascular ectasia, angiodysplasia, Dieulafoy lesion or watermelon stomach, are varied and possibly reflect morphological heterogeneity of overlapping entities. These lesions are usually diagnosed at endoscopy and/or by angiography or other imaging modalities and treated locally by cauterization or embolization. In a subset of cases, a biopsy is performed and, less frequently, a surgical resection is required to control gastrointestinal hemorrhage. Therefore there are few data in the recent literature on the histomorphological characteristics of such lesions.

The purpose of this study was to report the morphological and clinical characteristics of gastrointestinal benign vascular lesions in a series of 27 patients treated at the same institution.

Methods

All cases with the diagnosis of angioma, lymphangioma, hemangioma, arteriovenous malformation, vascular malformation of the gastrointestinal tract were retrieved from the database of the Department of Pathology, Johns Hopkins Medical Institutions. All available slides (hematoxylin and eosin stains, PAS, and Mas-

son trichrome), were retrospectively analyzed by the authors. Clinical and pathological data were collected from the clinical and pathology charts.

A total of 27 lesions, diagnosed between 1989 and 2010, were retrieved. In 12 patients, the diagnosis was hemangiolymphangioma (HLA; hemangioma or lymphangioma), and in 15 patients the diagnosis was arteriovenous vascular malformation (VM; vascular malformation or arteriovenous malformation). Limited results of imaging studies were available. Hemangiolymphangioma was defined as a proliferation,[2] or network [4] of vascular spaces or vessels of varied nature (lymphatics, capillaries, veins or venules, arteries or arterioles), lined by a benign endothelial lining with intervening connective tissue stroma, and forming a tumor [1]. Hemangiomas and lymphangiomas displayed an interanastomosing network of (usually) small vessels. Some were composed of purely blood vessels (hemangiomas) or purely lymphatics (lymphangiomas), whereas others were composed of an admixture of the two [2,4]. Vascular malformations were defined by the presence of clusters of irregular, distorted vessels, some of indeterminate nature (vein versus artery), with or without a feeding vessel or shunt vessels, frequently transmural [2,5]. Some observers regard VMs as congenital lesions and use the term "angiodysplasia" to refer to acquired lesions [2,3], such cases had been coded as "vascular malformations" in our archives.

Immunohistochemistry was performed on representative sections of lesions coded as hemangiolymphangioma with antibodies directed against CD31 (Ventana, clone JC70, prediluted, Tucson, AZ, USA), Glut-1 (Ventana, rabbit monoclonal, prediluted, Tucson AZ, USA) and D2-40 (Dako, anti-podoplanin, clone D2-40, Carpinteria, CA, USA). The percentage of stained intralesional vessels and the intensity of staining were determined (0 to 3, 3 being the intensity of staining in normal vessels for CD31 and D2-40 and in erythrocytes for Glut-1).

Differences between the clinico-pathological characteristics of VM and HLA were studied using the Fisher's, chi squared, or Student t tests (Medcalc v11.1.1, Belgium). Although the follow-up standards changed during the study period (1989-2010), we attempted to perform survival statistical analysis. The relationship between overall survival (defined as time between the gastrointestinal biopsy or resection of the first vascular lesion with available specimen, and date of last consultation or death) and lesion type was determined by using the Kaplan-Meier method and the Logrank test. The 3 patients without available post-surgical clinical data were excluded from this analysis (1 patient with HLA and 2 patients with VM). The accepted level of statistical significance for all tests was $p<0.05$.

Results

Gastrointestinal hemangiolymphangiomas

The clinicopathologic features of the 12 patients with hemangiolymphangiomas are summarized in **Table 1**.

Women and men were equally affected and most of the patients were of non-Asian origin (11/12; 92%). All lesions were diagnosed in adult patients; the age at time of diagnosis ranged between 36 and 89 years. The HLAs were associated more frequently (45%) with non-specific signs and symptoms such as vomiting, dyspepsia, abdominal pain or were incidental findings. Gastrointestinal bleeding was noted in 27% of the patients and anemia in 18% of the patients. Tumors were most commonly located in the small intestine but also in the colon (8 and 4 patients, respectively), with cecal lesions in 2 of the 4 patients with colon HLAs. None of the patients, including those presenting with gastrointestinal bleeding, required blood transfusion. In all but one patient, the diagnosis was established on biopsy and no additional intervention was necessary.

The follow-up period ranged from 2 and 110 months (median 19 months). In 2 patients, additional, subsequent gastrointestinal vascular lesions arose at 2 and 3 years after the diagnosis of the initial lesion. The subsequent lesions were unavailable for histological analysis. One patient died of metastatic lung cancer.

Several associated conditions, tumoral or not, were present in patients with HLA (**Table 2**): cardiovascular disease was noted in 8 patients, autoimmune disorders and tumors in 3 and 6 patients, respectively. None of the associated tumors was of vascular origin. Two patients were diagnosed with vascular aneurysms: cerebral at 6 years after the gastrointestinal lesion (in a patient who also manifested retinal vein

Table 1. Characteristics of the 12 patients with digestive hemangiolymphangiomas and of the 15 patients with gastrointestinal vascular malformations

	Hemangiolymphangioma N=12	Vascular malformation N=15
Age	58.5 years (36-89)	60 years (5-89)
Gender		
Women	6	9
Men	6	6
Race		
Black	5	4
White	6	10
Other	1	1
Clinical complaint		
Gastrointestinal bleeding	3	13
Anemia	2*	2**
Non-specific (abdominal pain, vomiting, diarrhea, dyspepsia)	5	0
Asymptomatic	1	1
NA	1	1
Location		
Stomach	0	3
Small intestine	8	1
Colon	4	2
Small intestine and colon	0	8
Stomach and intestine	0	1
Size (for polypectomy or resection)	0.5-3.5 cm	0.6-3 cm
Type of resection		
Biopsy	7	1
Polypectomy	4	0
Surgical	1	14
Transfusion	0	3
Follow-up		
Overall survival (months)	20 (2-110)	26 (<1-159)
Death	1	5
Subsequent gastrointestinal vascular lesions	2	3

NA: non-available data; Anemia was associated to asthenia in one patient with hemangiolymphangioma (*) and in 2 patients with vascular malformation, to gastrointestinal bleeding (**).

obstruction), and abdominal aortic, 2 years before the gastrointestinal vascular lesion. In the first mentioned patient, a 62-year old white man, the clinical history revealed scleroderma, Raynaud phenomenon and dry-eye syndrome as well as several benign tumors: choroid plexus nevus, colon adenoma and hyperplastic polyp. The HLA arose in the colon and was detected

Table 2. Associated conditions in the 12 patients with digestive hemangiolymphangiomas and of the 15 patients with gastrointestinal vascular malformations

	Hemangiolymphangioma N=12	Vascular malformation N=15
Arterial hypertension	7	5
Extradigestive vascular lesions		
Aneurysm	2	3
Aortic stenosis	0	3
Cardiac malformation	0	1
Blood disorder		
Thrombopenia	0	2
Hemophilia C	1	0
Thalassemia	1	0
Unspecified	0	1
Autoimmune disease		
Rheumatoid arthritis	0	2
CREST syndrome	0	1
Scleroderma	1	0
Crohn disease	0	1
Henoch-Sconlein purpura	0	1
Multiple sclerosis	0	1
Myasthenia gravis	1	0
Psoriasis	0	1
Hashimoto thyroiditis	1	0
Gout	1	1
Diabetes	0	3
Diverticulosis	1	4
Cirrhosis (clinically diagnosed)	1 (HBV related)	2 (cryptogenic)
Obesity	1	1
Asthma	0	2
Tumor		
Gastrointestinal (colon)		
Adenoma	1	2
Hyperplastic polyp	1	0
Adenocarcinoma	0	1
Extra-gastrointestinal		
Choroidal nevus	1	0
Cutaneous nevus	0	2
Basal cell carcinoma	2	0
Lipoma	1	0
Liposarcoma	0	1
Breast cancer	1	1
Prostate adenoma	0	1
Prostate cancer	1	1
Lung cancer	0	1
Hepatocellular carcinoma	1	0
Steroid treatment	0	3
Radio or chemotherapy	2	1

Table 3. Comparison of morphological features of vascular malformations and hemangiolymphangiomas of the gastrointestinal tract

	Vascular malformation N=15	Hemangiolymphangioma N=12
Mucosa		
Ulcer	12	0
Lymphatic cluster	0	8
Capillary cluster	0	1
Indeterminate vessels	4	0
Submucosa		(n=10)*
Vascular cluster	15	10
Feeder vessel	11	1
Fibrosis	14	9
Muscularis propria	(n=12)*	(n=1)*
Vascular cluster	4	1
Feeder vessel	12	1
Fibrosis, hypotrophia	9	1
Subserosa	(n=12)*	(n=1)*
Vascular cluster	6	1
Feeder vessel	10	1
Fibrosis	4	1
Vascular lesions		
Hemorrhage	10	2
Fibrosis (damaged vessel)	6	0
Thrombosis	9	2
Shunt lesion	9	1
Aneurysm-like cavity	6	4
Wall excrescence/tuft	13	5
Dissection-like lesion	4	1
Arterialized vein	11	0

The numbers in brackets correspond to the specimen with available submucosa or muscularis propria or subserosa.

during an evaluation for anemia. The second patient, an 89-year old white man, also had myasthenia gravis and factor XI deficiency (hemophilia C). In this patient, the biopsied lesion was colonic, detected during an evaluation for diarrhea, and subsequent additional vascular lesions were clinically diagnosed in the stomach and jejunum but no biopsies were obtained.

Association with an autoimmune condition was observed in a patient with arterial hypertension (in addition to the above-noted man with Raynaud's phenomenon and aneurysms), a 60-year old woman with a duodenal angioma detected during evaluation for emesis. This patient had a clinical history of Hashimoto thyroiditis, thalassemia minor, and arthritis as well as of breast carcinoma and cutaneous basal cell carcinoma.

The macroscopic appearance of HLA was polypoid in 5 patients, and for lesions that were resected (polypectomy or surgical resection) the size ranged between 0.5 and 3.5 cm; median 0.7 cm (**Table 1**). On microscopy, the lesions consisted of a proliferation of varied vessel types (lymphatics, capillaries, veins), located in the submucosa (1 patient), mucosa (1 patient) or both (9 patients) (**Table 3**) (**Figure 1**). The predominant lesional vessel type was lymphatic, capillary or venous (5, 2 and 3 lesions, respec-

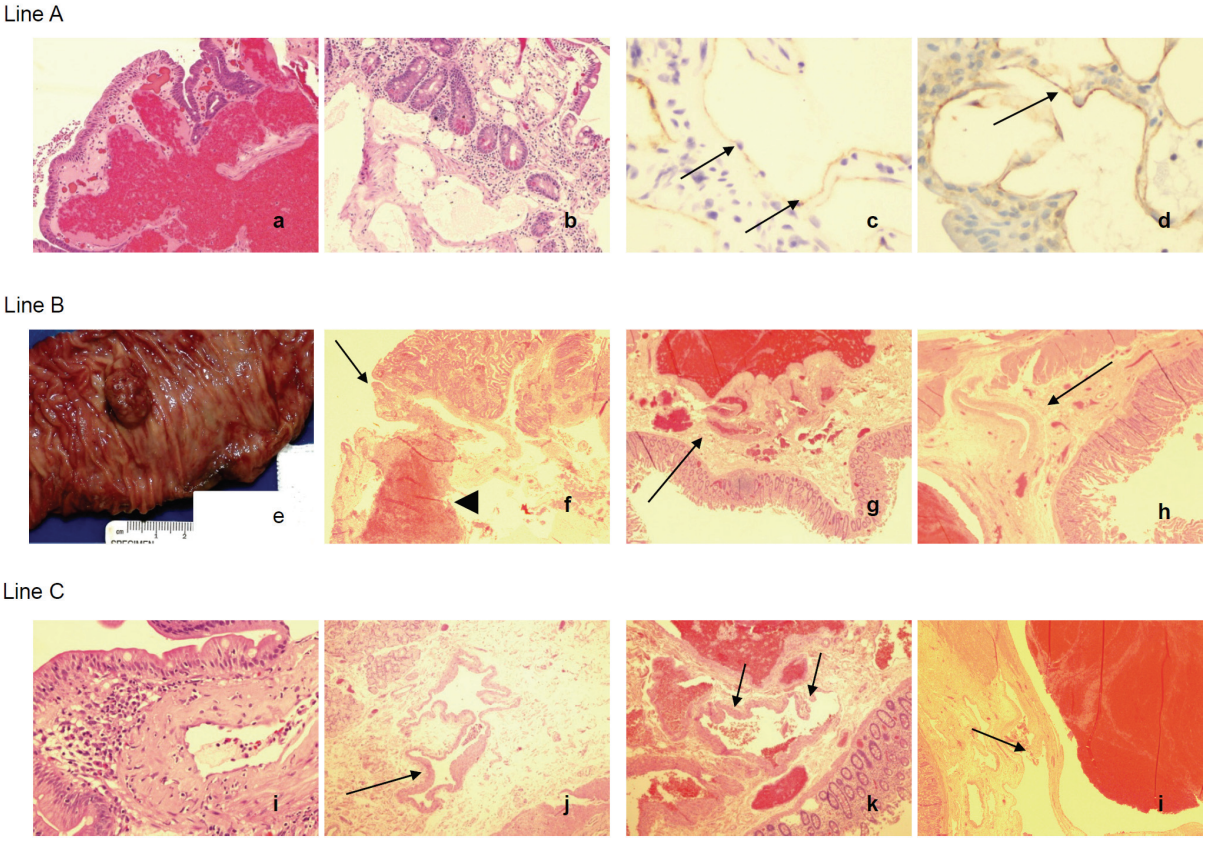

Figure 1. Line A. Intestinal hemangiolymphangiomas. Hemangiolymphangiomas consisted of mucosal and submucosal proliferations of capillary-type blood vessels (a, hematoxylin and eosin stain, original magnification x10), and of lymphatic-type vessels (b, hematoxylin and eosin stain, original magnification x10). D2-40, as well as CD31 were expressed by endothelial cells (arrows) in the lymphatic proliferations (d and e, hematoxylin and eosin stain, original magnification x40). Line B. Gross view and microscopic features of an intestinal vascular malformation. Macroscopically, there was a hemorrhagic polypoid intestinal lesion (e). On microscopy, the lesion was ulcerated (arrow), thrombotic and hemorrhagic (arrowhead) (f, hematoxylin and eosin stain, original magnification x2). There was a vascular submucosal cluster (arrow) (g, hematoxylin and eosin stain, original magnification x2) with a large vessel (arrow) (h, hematoxylin and eosin stain, original magnification x4). Line C. Abnormal vascular lesions in vascular malformations. Thick walled vessels were observed in the mucosa on biopsy specimen (i, hematoxylin and eosin stain, original magnification x40). The vascular clusters in the submucosa contained vessels of indeterminate nature or shunt vessels (arrows) (j and k, hematoxylin and eosin stain, original magnification x10) or aneurysm-like dilatations (arrow) (l, hematoxylin and eosin stain, original magnification, x4).

tively). Vascular cavities (dilation with irregular contours) were observed in 5 cases and striking vascular ectasia (dilation) was observed in 4. The submucosal HLA were associated with mucosal lymphangiectasias. Mucosal hemorrhage was observed in 2 patients (one of the patients having undergone radiotherapy for prostate cancer), whereas there was mucosal capillary reactive congestion in normal capillaries away from the lesion in all biopsies. Thrombosis was noted in 2 cases (one patient with hepatitis C and one patient undergoing radiotherapy for prostate cancer). There were no signs of vasculitis, hypertensive portal gastro- or colopathy or radiotherapy induced vascular changes.

In the patient treated by surgical resection, a 38 -year old woman with a history of hepatitis C viral hepatitis, the small intestinal submucosal lesions were associated with tortuous, abnormally large veins of the muscularis propria (and thus displayed overlapping features with vascular malformations discussed below).

On immunohistochemistry, all lesions were lined by CD31 positive, Glut-1 negative cells (**Figure**

Table 4. Comparison of main morphological features of the main clinically relevant and of the "background", incipient vascular malformation lesions diagnosed on surgical resection specimen (14 patients)

	Clinically relevant, ulcerated vascular malformation N=12	"Background", incipient vascular malformation N=14
Location		
Stomach	3	4
Small intestine	3	3
Colon	6	1
Small intestine and colon	0	6
Intralesional hemorrhage	10	3
Mucosal lesions		
Ulcer	12	0
Vascular cluster	0	0
Indeterminate vessel	3	1
Submucosa		
Vascular cluster	12	14
Feeder vessel	10	11
Fibrosis	11	12
Muscularis propria		
Feeder vessel	4	12
Vascular cluster	1	3
Fibrosis or hypotrophy	6	5
Subserosa		
Vascular cluster	1	6
Feeder vessel	5	7
Fibrosis	1	3

1). CD31 expression was heterogeneous in 5 lesions. The D2-40 antibody (anti-podoplanin) was expressed to various extent in tumoral vessels (2-70%) regardless of whether the morphologic features were those of hemangiomas or lymphangiomas, and the staining intensity was less than in normal, physiologic lymphatic channels in all cases (including those with morphologic features of lymphangiomas). Expression in the lining of vascular cavities or ectatic vessels was heterogeneous, observed in 5 of the 8 positive cases.

Gastrointestinal vascular malformations

Gastrointestinal vascular malformations were more frequent in women and in white patients (**Table 1**). These lesions were rarely asymptomatic (1 patient), and frequently associated with gastrointestinal bleeding (13/14 patients, 93%; 1 patient with no available data). Anemia was diagnosed in 2 patients (14%), both patients having gastrointestinal bleeding. Blood transfusions were required in 3 patients; vascular lesions were subsequently diagnosed in 2 of these patients. All but one patient were treated by surgical resection. In 4 cases, lesions were located in the stomach, all requiring surgical resection. Among intestinal lesions, the small intestine and the colon were equally affected. Only 1 patient had a cecal lesion.

On macroscopic evaluation, lesions consisted of congestive streaks measuring between 0.6-3

cm; median 1.3 cm. The largest lesion (3 cm) had polypoid features (**Table 1**) (**Figure 1**). In 5 patients, lesions were not detected macroscopically, requiring extensive sampling to identify. On microscopy, lesions consisted of submucosal clusters of vessels of varied nature (arteries/arterioles, capillaries, veins/venules, lymphatics) (**Table 3**) (**Figure 1**).

The predominant vessel type was of arterial-type (7 patients), venous type (2 patients) or both (2 patients), or of capillary type (1 patient) and all cases showed abnormally formed vessels of varying wall-thicknesses. In 11 patients there was a feeder vessel identified in the submucosa, muscularis propria or in the subserosa. The mucosa was ulcerated in 12 cases, most ulcers occurring in association with colon VM. The ulcer depth was variable. Mucosal erosion or ulceration was observed in 5 cases. In 3 cases the ulcer attained the submucosa and in 4 cases penetrated into the muscularis propria. In cases in which the mucosa was intact, there were prominent thick-walled mucosal capillary-sized vessels identified in 4 cases, a feature not encountered in HLA. In other cases, there were no angioma-like clusters in the mucosa, but they were encountered in the muscularis propria and subserosa (4 and 6 cases, respectively). There were no signs of diabetic angiopathy or vasculitis or radiotherapy induced vascular changes.

Multiple VMs were identified in several patients either in the same resection specimen, in several specimens or in a resection specimen and at subsequent endoscopy (11, 1 and 1 patients, respectively). Lesions detected at some distance from the clinically relevant VM, when encountered in the surgical resection specimen, consisted of the same type of vascular lesions as the clinically relevant lesion (**Table 4**).

These lesions, probably corresponding to incipient VMs, were located apart from the clinically relevant VM, in both the small and large intestine, and were characterized by lack of a coexisting ulcer, and less frequent presence of intralesional hemorrhage and prominent mucosal capillaries.

The vascular malformations harbored several types of vessel abnormalities: shunt vessels, aneurysm-like cavities, arterialized veins, or vascular wall tufts (9, 6, 11 and 13 cases, respectively). Some vessels resembled those of the type related to high pressure in rectal hemorroids. Complications of the lesions consisted of lesional hemorrhage and vascular thrombosis (10 and 9 cases, respectively) (**Figure 1**).

Four cases were initially diagnosed as Dieulafoy's lesion or Dieulafoy's lesion-like; three were classical gastric lesions and the last involved the colon. In patients with Dieulafoy's lesion, vascular alterations in the muscularis propria and subserosa both in the main lesion and at distance in the resected stomach or colon, were similar to those noted for patients with VM (**Table 5**). The resection specimen diagnosed as Dieulafoy's lesion also showed submucosal vascular clusters but these lesions were less striking than the so-called "persistent caliber artery" and therefore we considered the Dieulafoy's lesions as a type of VM.

Biopsies obtained prior to surgical resection were available for 2 patients (performed within the month before surgery). The lesions were non-specific but suggestive of VM and showed mucosa ulceration (1/2 cases), lymphatic clusters (1/2 cases), hemorrhage (1/2 cases), and thrombosis (1/2 cases). These lesions, except the vascular cluster, were observed both on biopsy and surgical resection specimens.

In 3 patients, additional VM manifested over a period of 1, 2 and 6 years after the diagnosis of the initial gastrointestinal VM; in 2 patients these lesions were resected. The follow-up time ranged from <1 and 159 months (median, 26 months), and 5 patients died during the follow-up period. For the patient with a "polyp" biopsy, the condition had not recurred or caused additional morbidity at 43 months.

Thrombocytopenia was diagnosed in 2 patients and idiopathic thrombophlebitis (with lung emboli) in one patient.

There was a history of previous gastrointestinal surgical resection related to gastrointestinal bleeding in 2 patients (but surgical specimens were not available for review) and one other patient had a colectomy for colon adenocarcinoma.

Several clinical associations, syndromic or otherwise, non-tumoral or tumoral, were observed (**Table 2**): cardiovascular in 8 patients, autoim-

Table 5. Comparison of morphological features of vascular malformation and classical gastric Dieulafoy lesions

	Vascular malformation N=12	Dieulafoy lesion N=3
Mucosa		
Ulcer	9	3
Lymphatic cluster	0	0
Capillary cluster	0	0
Indeterminate vessels	3	1
Submucosa		
Vascular cluster	12	3
Feeder vessel	8	3
Fibrosis	11	3
Muscularis propria	(n=11)*	(n=3)*
Vascular cluster	4	0
Feeder vessel	9	3
Hypotrophy or fibrosis	7	2
Subserosa	(n=10)*	(n=3)*
Vascular cluster	5	1
Feeder vessel	7	3
Fibrosis	3	0
Vascular lesions		
Hemorrhage	7	3
Fibrosis (damaged vessel)	4	2
Thrombosis	7	2
Shunt lesion	8	1
Aneurysm-like cavity	6	0
Wall excrescence/tuft	11	2
Dissection-like lesion	4	0
Arterialized vein	10	1

*The numbers in brackets correspond to the specimen with available submucosa or muscularis propria or subserosa.

mune in 6 patients and tumoral in 7 patients. Association with a malformative lesion (development defect), cardiac *foramen ovale* was present in a 75 year old man with colonic and small intestinal VM, and several other patients had degenerative age-related vascular lesions (cerebral and cutaneous small vessel disease, carotid and renal artery stenosis) as well as arterial hypertension, osteoarthritis, prostate carcinoma, colon adenoma, and lung cancer.

Other observed vascular lesions included aortic sclerosis, aortic stenosis and aortic aneurysm (1, 3, 3 respectively). The 2 patients with aortic stenosis and abdominal aneurysm also had thrombopenia in a context of cryptogenic cirrhosis, and co-existing intestinal conditions (diverticulosis in one case and colon adenocarcinoma in the other).

A third patient had an ophthalmic aneurysm, associated with small vessel disease of the myocardium and myelomalacia. Aortic stenosis was unassociated with other conditions in another patient but aortic sclerosis was observed in 1 patient with rheumatoid arthritis, esophageal dysmotility, idiopathic lung thrombemboli, and soft tissue and connective tissue tumors (liposarcoma, chondrodermatitis nodularis).

In two patients with systemic blood disorders, there was intralesional thrombosis within the VM.

Autoimmune disease was present in 6 patients, but the type of associated disorder was varied: CREST syndrome, rheumatoid arthritis, Crohn disease, Henoch-Schonlein purpura/vasculitis, multiple sclerosis and psoriasis. In the patients with CREST syndrome and with psoriasis, VM were "recurrent" and required blood transfusions. In both cases diverticulosis was associated. In the patient with Henoch-Schonlein purpura, the lesion was hemorrhagic, ulcerated and thrombi were observed.

Neoplasms were observed in 7 patients, none of vascular origin. In 2 patients there were benign tumors, in 2 malignant and in 3 patients both benign and malignant.

Steroid treatment was administered to 4 patients, systemic in 3 patients, and local in 1 patient. One patient with prostate adenocarcinoma had radiotherapy.

Comparison between gastrointestinal hemangiolymphangiomas and vascular malformations

When comparing the clinical and morphological features of HLAs and VMs, VM were more frequently associated with gastrointestinal bleeding ($p<0.01$) and associated with mucosal ulcer ($p<0.01$) (**Table 1**). There were no significant differences related to age, gender or race between the 2 groups of patients. Not surprisingly, HLA size was significantly smaller than that of VM ($p<0.01$). All gastric lesions were VMs. In one patient, gastric and intestinal lesions were diagnosed 2 years after diagnosis of the intestinal HLA, at endoscopy (no histologic material was available for review). Intralesional hemorrhage and vascular thrombosis were more frequently associated with VM ($p=0.02$ and $p=0.05$, respectively) (**Table 3**). Characteristic mucosal vascular abnormalities in VM consisted of abnormal thick-walled vessels but these mucosal lesions were observed in only 4 of the VM patients (**Figure 1**). Mucosal lymphatic clusters were typical of HLAs ($p<0.01$). Submucosal feeder vessels were a constant finding in VM as compared to HLA ($p<0.01$), but this finding might also be related to the type of specimen and sampling since resections were more likely in patients with VM. Among vessel abnormalities, shunt vascular lesions, wall tufts (excrescences) and arterialized veins were more frequently encountered in VM than in HLA ($p=0.01$, $p=0.04$ and <0.01, respectively) whereas aneurysm-like cavities were observed in both lesion types. Vascular fibrosis and damaged vessels were observed only in VM ($p=0.02$).

There was no statistically significant difference between overall survival in the 2 patient groups (Logrank $p=0.27$, hazard ratio 0.35, 95% CI 0.06 to 2.21). Although the median overall survival was shorter in HLA patients as compared to VM patients (20 *versus* 26 months), death was more frequent in the VM patients group but was related to comorbidities rather than to the vascular lesions themselves.

Discussion

In this study we report the morphological and clinical characteristics of a large series of gastrointestinal vascular malformations and of hemangiolymphangiomas.

Vascular malformations are usually classified by angiography [5], or other imaging techniques [6]. Those in the skin and soft tissues tend to arise in children [7], where they can be difficult to distinguish from intramuscular hemangiomas [8] or "angiomatosis" [9] (distinctions which might be arbitrary), such lesions in the gastrointestinal tract are both rarer and encountered in adults. There is tremendous overlap in reported series between gastrointestinal tract angiodysplasia, vascular ectasia, arteriovenous malformations, and even angiomas of the gastrointestinal tract or aneurysm [2,3,10-14]. To some extent, these different terms may reflect topographic peculiarities of a single entity rather than different specific entities. For example, the Dieulafoy lesion, a variant of gastrointestinal vascular malformation [15], more recently designated as "caliber persistent artery" [16,17], is defined as gastric hemorrhage due to ulceration of a large tortuous arteriole and the overlying mucosa. Angiodysplasia defines a clinical, endoscopical entity in which the underlying morphological lesion consists of ectasia of normal preexisting intestinal submucosal veins and overlying mucosal capillaries [10,13,14,18,19]. Moore et al considered such lesions as type 1 vascular malformations [20]. Another clinical entity is gastric antral vascular ectasia (GAVE) or "watermelon stomach" in which patients present with gastrointestinal blood loss and iron-deficiency anemia, have a distinctive endoscopic appearance of parallel erythematous

gastric antral folds, and, on microscopy display dilated and thrombosed capillaries of the gastric antral lamina propria and with associated fibromuscular hyperplasia [21-26]. Arguably GAVE differs from the other entities by being defined, in some respects, by the presence of fibrin thrombi [27], but it remains a lesion characterized by abnormal lamina propria vessels. All these terms are currently used but perhaps a unifying term, especially appropriate for lesions diagnosed on surgical specimens, is arteriovenous malformation [5] or the less specific term vascular malformation. Since arteriovenous features cannot always be documented histologically, we have used the term "vascular malformation".

In this study, we report the characteristics of 15 patients having gastrointestinal VMs, 14 of which treated by surgical resection. We did not include biopsied mucosal lesions coded as "GAVE" since such lesions have been attributed to mucosal prolapse in a specific location [27], although one of the cases displayed vascular thrombi in a lesion clinically regarded as an antral vascular malformation on imaging. The study of surgical resection specimen allowed us to identify lesions at different stages of evolution, both at a late, clinically relevant stage and at an early, microscopic stage. The lesion of clinical relevance in VM was the presence of ulcers of varying depth which were frequently associated with hemorrhage and thrombosis. The origin of hemorrhage at this stage of disease, whether from large submucosal feeder vessels or from the capillary web was difficult to establish based on a retrospective microscopy analysis. However in the surgical specimens we studied, in which we had full sections available for review, we were able to confirm the presence of large feeder vessels and vascular clusters in the muscularis propria and serosa, often with irregular vascular walls or fibrosis. Another morphological feature we noted was the presence of multifocal VM remote from the clinically relevant, ulcerated lesions. These lesions differed from the clinically relevant lesions by the lack of ulcer and intralesion hemorrhage. The presence of multiple lesions, as previously noted by Marangoni [28] and Liao [29], does not seem to impact on the decision for surgical resection as much as the severity of clinical manifestations, namely gastrointestinal bleeding. Some authors may have interpreted all of the adult lesions in our series as angiodysplasias rather than vascular malformations *per se* [2], although the adult lesions displayed histologic overlap with the 2 pediatric VM in our series. The two pediatric lesions were classic VM similar to those described in the somatic soft tissue and both displayed bizarre-appearing vessels and arterialized veins.

The pathogenesis of VM is probably complex since several vessel wall lesions can complicate hamartomatous vascular anomalies. Arterialization of veins, wall tufts or aneurysm-like cavities resulting in what has been previously reported as a "dysplastic vessels" [2,16], or "indeterminate vessels" were all observed in the majority of our cases. Although we did not demonstrate significant relationships between these vascular structural abnormalities and the associated systemic autoimmune, metabolic, tumoral or vascular conditions or medications, or coexistence of gastrointestinal disorders (diverticulosis, tumors or post-surgical reparative lesions), we cannot exclude an interaction, more probable for associated cardiovascular conditions, that might potentiate clinically significant gastrointestinal bleeding. Therefore, the diagnosis at a non-surgical, clinically irrelevant stage of gastrointestinal VM would be necessary to forestall significant hemorrhage.

Our retrospective study, performed on surgically resected specimens comparing clinically relevant lesions with incipient, "background" lesions, did not allow us to identify histological features indicative of an evolution towards ulcer and clinically significant bleeding. However, some features seen on mucosal biopsies may help distinguish HLA from VM. This distinction is of some clinical relevance since surgical resection was required for 14/15 (93%) VM patients as compared to 1/12 (8%) HLA patients. Mucosal thick-walled capillaries were observed only in VM specimens, although, unfortunately only 27% of the VM displayed this feature. In contrast mucosal HLA was characterized by collections of mucosal lymphatic. Another morphological feature that may help differentiate VM from HLA is the presence of submucosal feeder vessels in VM, but finding sufficient submucosa to assess this feature is unusual on endoscopic biopsies [30].

In contrast to VM, HLAs are defined as detectable masses [5], although several authors consider angioma as a misnomer for hamartoma

[4, 31]. These benign vascular tumors are rare in the gastrointestinal tract, River et al [32] reported 127 angiomas in their series of 1399 benign neoplasms of the small intestine. More recently, the largest series of sporadic cases comprised 4 colorectal [33], and 4 small intestinal cases [34]. In our series, the 12 HLA were solitary lesions of adults and were only rarely associated with gastrointestinal bleeding. On microscopy, the lesions were mainly submucosal, with a lesser mucosal component, and they lacked associated mucosal ulceration. Abnormal, aberrant vessels such as shunt vessels, arterialized veins, vascular wall tufts, aneurysm-like cavities or intralesion hemorrhage and thrombosis were not frequent in or characteristic of HLA. A lymphatic component was observed in the majority of lesions. Interestingly, podoplanin expression (using D2-40) was heterogeneous, ranging between 2-70%. Although only one case in our series required surgical resection, follow-up of HLAs is probably indicated since hemorrhagic complications or recurrent/multiple subsequent lesions may occasionally arise. Not surprisingly, Glut-1 labeling was absent in all of the studied cases. The latter has been reported as a marker that helps distinguish vascular malformations from juvenile hemangiomas (that tend to regress) as it is expressed by juvenile hemangiomas and not by vascular malformation [35]. However, Glut-1 is absent in some lesions that are traditionally classified as neoplasms with vascular differentiation [36].

In this series, none of the patients with gastrointestinal HLA manifested angiomas outside the digestive tract. Two patients had arterial aneurysms. One of the patients had a cerebral aneurysm, scleroderma, Raynaud phenomenon and dry-eye syndrome [37], and the other patient had an abdominal aortic aneurysm, hemophilia C (factor XI deficiency) and myasthenia gravis (including esophageal spasm). There are few data on the impact of factor XI deficiency on vascular lesions [38], and whether this condition could be an exacerbating factor for HLA bleeding although it has been suggested in 2 patients with cerebral aneurysms [39].

The pathogenesis of these associations is difficult to establish in this series of sporadic gastrointestinal HLAs and VMs. However, associations between VM and vascular or autoimmune connective disorders have been reported [5,40]. The association of gastrointestinal HLA or VM with arterial aneurysms, aortic stenosis and blood disorders, without a specific time sequence in their occurrence, was observed in 3 of the patients, and its possibly fortuitous nature is worth exploring. Although observed in more than one third of the patients, an association with autoimmune disorders is difficult to establish because of the heterogeneity of associated autoimmune disorders in our series, some of them previously unreported to our knowledge (such as hemophilia C or scleroderma and intestinal HLA). Similarly, a unifying process linking gastrointestinal VM and HLAs with other tumors, all non-vascular, is not clear. Of clinical relevance would be the association of a hemorrhagic VM in the patient with Henoch-Schonlein purpura, an association previously not reported to our knowledge, although gastrointestinal intramural hematomas have been reported in a patient with this condition [41,42].

In conclusion, we report the morphological and clinical characteristics of a relatively large series of rare benign vascular lesions of the gastrointestinal tract: hemangiolymphangioma and vascular malformation. Although our findings are somewhat limited by the retrospective nature of the work, the case heterogeneity and the rarity of these lesions at surgical stage [2-4], our study allows us to propose distinguishing morphological features which could help in differentiating the 2 lesion types. Ulcer, hemorrhage, thrombosis and presence of aberrant vessels (shunt vessels, wall tufts/excrescences and arterialized veins) favor the diagnosis of VM. Moreover, mucosal abnormal vessels were observed only in VMs, whereas HLAs were associated with mucosal lymphatic clusters, these features being helpful on biopsy specimen evaluation. The results of our study also suggest that gastrointestinal bleeding were associated with VM and required surgical resection, and that larger lesion size was a feature of VM. Coexistence of other clinical conditions such as cardiovascular disease, encountered in association with both lesion types, might exacerbate a tendency towards hemorrhage. Therefore, and given the fact that “background”, multiple, incipient VMs may be frequently present along the gastrointestinal tract, diagnosis at a pre-surgical stage and a specific follow-up would be optimal for patients with gastrointestinal vascular malformations and hemangiolymphangiomas.

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