Clinicopathological characteristics and prognosis of gastrointestinal vascular tumours

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To evaluate the clinicopathological characteristics and prognosis of gastrointestinal vascular tumours. By reviewing the information from the electronic medical record system and pathology database of Hangzhou First People's Hospital affiliated with Zhejiang University School of Medicine and Jiaxing First People's Hospital from June 2008 to December 2019, 31 patients pathologically diagnosed with vascular tumours were included in this study. The age of onset, sex differences, clinical manifestations, imaging and endoscopic characteristic manifestations, pathological characteristics, treatment methods and prognosis were analysed. The pathological classification was haemangiolymphangioma, haemangioma, and lymphangioma in 8, 14, and 9 cases, respectively. The age of onset was 44–66 years, with no significant difference according to sex (P = 0.583); 32.26% (10/31) of patients had no noticeable symptoms, 37.5% (12/31) of patients had gastrointestinal bleeding, and 6.45% (2/31) of patients, all with lymphangioma, had intestinal obstruction. The lesions were located in and below the duodenum. Endoscopy showed colour differences. Both endoscopic and surgical treatments were safe and effective. The mean survival time was 57.06 ± 35.64 months. Regarding vascular tumours without typical symptoms, the main pathological classification is haemangioma. Vascular tumours are often clinically identified because of bleeding or obstruction and can be treated with endoscopy or surgery. Clinical follow-up is recommended because no invasive manifestations or instances of recurrence were observed.

Vascular tumours (VTs) are rare, with an incidence rate of 0.12% to 0.28% among all digestive diseases1, and are a class of benign tumours originating in mesenchymal tissue. The pathological types include haemangiolymphangioma (HL), haemangioma (H) and lymphangioma (L), which are common in children and adolescents2 and rare in adults; multiple VTs can occur in the head, neck and limbs3, but VTs in the digestive tract are rare. A few cases are classified as "intussusception"4 or "anaemia of unknown cause"5. These reports and lack of relevant systematic research, because of the lack of understanding of this disease, have led to frequent misdiagnosis of the disease and unreasonable treatment plans. To clarify the clinical characteristics of vascular tumours and provide the basis for clinical diagnosis and treatment, this study retrospectively analysed the clinical data of 31 patients with VTs diagnosed at the Hangzhou First People's Hospital affiliated with the Zhejiang University School of Medicine and First People's Hospital of Jiaxing City from June 2008 to December 2019, as reported below.

Materials and methods

Research subjects. Thirty-one patients diagnosed with VTs from June 2008 to December 2019 at the Hangzhou First People's Hospital affiliated with the Zhejiang University School of Medicine and Jiaxing First People's Hospital were divided into 3 groups according to pathology, as follows: haemangiolymphangioma group (HL group; 8 cases); haemangioma group (H group; 14 cases); lymphangioma group (L group; 9 cases). Differences in sex, clinical manifestations, characteristic imaging and endoscopy findings, surgical pathological characteristics, treatment methods and prognosis were examined.

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**Results**

**Age of onset.** The age range was 19–84 years, with an average age of 52.94 ± 18.18 years. No statistically significant difference was found in the age of onset between the male and female patients (52.73 ± 17.42 vs. 53.13 ± 19.43, respectively; P = 0.583), with the age of onset ranging from 44 to 66 years (48.39%, 15/31).

According to the pathological type, the average ages in the HL, H, and L groups were 56 ± 13.26, 53.36 ± 20.92, 49.56 ± 18.75 years, respectively, and no significant difference was found among these three groups (F = 0.026; P = 0.773).

**Sex differences.** Among the 31 patients, 15 were male (48%). The ratio of male to female patients by pathological type was as follows (male/female): HL group, 2/6; H group, 7/7; L group, 6/3.

**Clinical manifestations.** Concerning the clinical manifestations, 32% (10/31) of the patients had no noticeable symptoms and were identified during a routine gastrointestinal examination; 23% (7/31) exhibited mild abdominal discomfort, such as mild abdominal pain and increased defecation frequency with occasional abdominal discomfort; 39% (12/31) exhibited signs of gastrointestinal bleeding, such as black stool, bloody stool, and dizziness and fatigue due to blood loss; 6% (2/31) exhibited signs of gastrointestinal obstruction, such as abdominal pain, nausea and vomiting. In addition to mild abdominal discomfort in the L group, 75% (3/4) of patients showed an increased defecation frequency, and no other pathological types were found in these patients. Symptoms of obstruction were found only in the L group, and the symptoms were typical signs of intestinal obstruction. No significant difference was found in the distribution of each pathological type (Fig. 1).

**Site of disease.** All VTs were found in or below the duodenum; 58% (18/31) of lesions were in the small intestine, and 42% (13/31) of lesions were in the large intestine. No significant difference was found in the distribution of each pathological type (Fig. 1).
Characteristics of blood indicators. The haemoglobin level was significantly higher in the L group than in the HL and H groups (P < 0.05; Table 1). No significant difference was found in the levels of white blood cells, neutrophils, platelets, or C-reactive protein among the three groups (P > 0.05), and the carcinoembryonic antigen (CEA) and alpha-fetoprotein (AFP) levels were in the normal range.

Morphological characteristics (shape, colour, and size) of the lesion. The average size of all the tumours was 16.71 ± 12.1 mm. The size of the tumours in the HL group (17.5 ± 9.89 mm), H group (16.93 ± 12.39 mm), and L group (15.67 ± 14.57 mm) was not significantly different (P = 0.052). Morphologically, H mainly developed laterally and was hemispherical (Fig. 2c), while HL and L showed no noticeable morphological characteristics and lateral development and globularity were dominant (Fig. 2a,b). HL was redder and whiter in colour, H was bright red and dark red (Fig. 3c,d), and L was milky white (see Fig. 2e,f; Table 2). More details are shown in the endoscopic images (Figs. 2 and 3).

Endoscopic and imaging features. White light images (WLIs) were evaluated. On endoscopy, HL showed characteristics of H and L and was difficult to distinguish. HL exhibited a complete adventitia or was thin like H (Fig. 2a,b). Additionally, white spots with flaky changes were observed by increasing the magnification of white granules (Fig. 3a), along with thick heterogeneous blood vessels and white opaque substances (Fig. 3b).

Table 1. Analysis of blood indexes in gastrointestinal VTs patients (N = 31). *L is significantly different from HL and H.

|                  | HL (N = 8) | H (N = 14) | L (N = 9) | F     | P    |
|------------------|-----------|-----------|----------|-------|------|
| Age (range), years | 56 ± 13.26 (30–77) | 53.36 ± 20.92 (19–84) | 49.56 ± 18.75 (22–71) | 0.026 | 0.773 |
| Sex              |           |           |          |       |      |
| Male, No         | 2         | 7         | 6        |       |      |
| Female, No       | 6         | 7         | 3        |       |      |
| WBC (10⁹/L)      | 5.74 ± 1.66 | 7.16 ± 2.95 | 6.71 ± 2.19 | 0.782 | 0.469 |
| N%               | 66.11 ± 10.91 | 70.79 ± 15.2 | 69.11 ± 7.9 | 3.189 | 0.059 |
| HB (g/L)         | 124.14 ± 23.88 | 87.3 ± 36.03 | 142.57 ± 15.61 | 4.317 | 0.025* |
| PLT (10⁹/L)      | 197.86 ± 48.19 | 172.7 ± 70.33 | 238.57 ± 84.81 | 2.659 | 0.091 |
| CRP (mg/L)       | 2.79 ± 3.03  | 7.6 ± 8.46  | 10.71 ± 17.67 | 0.227 | 0.799 |
| CEA (μg/L)       | 1.72 ± 1.27  | 2.5 ± 1.81  | 3.53 ± 1.65  |       |      |
| AFP (μg/L)       | 3.18 ± 1.62  | 2.7 ± 0.5   | 5.4 ± 3.96   |       |      |

Figure 1. Analysis of various types of gastrointestinal vascular tumors (VTs) by site. All VTs were found in or below the duodenum; 58.06% (18/31) of lesions were in the small intestine, and 41.94% (13/31) of lesions were in the large intestine. There was no significant difference in the distribution of each pathological type. (Font color corresponds to type).
Figure 2. Analysis of various types of gastrointestinal VTs by endoscopic pictures, which correspond to those of Fig. 5. (a) Hemangiolympangioma (HL) in the ileocecal region; b: HL in the terminal ileum; (c) Haemangioma (H) in the ileocecal region, H were mainly red, with the adventitia showing signs of blood filling; (d) H in the ileocecal region showing attached feces bleeding after flushing with normal saline; (e) Lymphangioma (L) in the ileocecal region; L were milky white, mucosal bulges with lateral changes; (f) Sigmoid lymphangioma; L presents an obvious cyst-like structure, containing lymph fluid.

Figure 3. Supplementary endoscopic pictures. (a) Duodenal HL mimicking a lymphangioma, white spots with flaky changes can be observed by increasing the magnification of white granules, see enlarged view; (b) Duodenal HL, along with thick heterogeneous blood vessels and white opaque substances, indicating a mixture of lymphatic and vascular components. (a, magnifying endoscope); (c) transverse colonic H showing striations; H sometimes has such red stripes; (d) H in the ileocecal region, H sometimes has such dark red color; dark red areas similar to signs of enveloping venous blood; (e) Duodenal H; Lack of obvious capsule structure, but ulcer surface, the clinical manifestation of this case is bleeding; (f) small intestinal hemangioma showing bleeding.
indicating a mixture of lymphatic and vascular components. Endoscopic ultrasound (EUS) showed that the hypoechoic shadows originated from the mucosal muscle layer and the submucosal layer, revealing an oval shape and internal separation (Fig. 4a). H lesions were mainly red, with the adventitia showing signs of blood filling (Fig. 2c). The adventitia was also thin and easily bledd after flushing (Fig. 2d), with striations (Fig. 3c) and dark red areas indicating enveloping venous blood (Fig. 3d) and a lack of a noticeable capsule structure but the presence of an ulcer surface. The clinical manifestation of this case was bleeding (Fig. 3e); The L lesions were milky white, and mucosal bulges showed lateral changes (Fig. 2e) or noticeable capsules (Fig. 2f). Noticeable H bleeding could be observed under the endoscope (Fig. 3f). Computed tomography (CT) of an angioma showed a low-density mass in the lower part of the duodenum, with multiple speckle-like high-density shadows; the size of the lesion was approximately 4.4 × 2.7 cm. Contrast-enhanced CT showed continuous uneven enhancement.

| Shape        | HL (N=8) | H (N=14) | L (N=9) | F     | P     |
|--------------|----------|----------|---------|-------|-------|
| Flake        | 1        | 0        | 2       |       |       |
| Lateral development | 3        | 3        | 3       |       |       |
| Hemisphere   | 4        | 8        | 2       |       |       |
| Spherical    | 0        | 3        | 2       |       |       |

| Colour       | HL (N=8) | H (N=14) | L (N=9) | F     | P     |
|--------------|----------|----------|---------|-------|-------|
| Dark red     | 1        | 2        | 0       |       |       |
| Red          | 5        | 12       | 0       |       |       |
| Pink         | 1        | 0        | 0       |       |       |
| Milky        | 3        | 0        | 9       |       |       |

**Table 2.** Morphological analysis of gastrointestinal VTs (N = 31).

**Figure 4.** Supplement endoscopic pictures, in order to show imaging. a: HL of the ileocecal vasculature, Endoscopic ultrasound (EUS) showed that the hypoechoic shadows originated from the mucosal muscle layer and the submucosal layer, revealing an oval shape and internal separation (Fig. 2a, EUS); b: Duodenum HL. Computed tomography (CT) of an angioma showed a low-density mass in the lower part of the duodenum, with multiple speckle-like high-density shadows; the size of the lesion was approximately 4.4 × 2.7 cm. Contrast-enhanced CT showed continuous uneven enhancement.

**Characteristic pathological manifestations.** HL: Irregular mucosal hyperplasia was observed in the lamina propria and submucosa. The inner wall was lined with a single layer of flat epithelium, and the cavity contained red blood cells or lymphatic fluid. Immunohistochemistry was positive for CD34 and/or D2-40 expression, suggesting the presence of proliferative vascular and lymphatic vessels (Fig. 5a,b). H: Clustered vascular hyperplasia in the submucosa of the intestine, lumen irregularity, partial dilation, and positive CD34 expression determined by immunohistochemistry all suggested H (Fig. 5c,d). L: The lymphatic vessels of the lamina propria of the intestinal mucosa showed significant proliferation, and the lumen contained lymphatic fluid. Immunohistochemistry was positive for D2-40 expression (Fig. 5e,f).

**Treatment and prognosis.** Of the 31 patients, 3 were followed up without treatment, and 14 had undergone endoscopic resection (EMR/ESD). Among them, 1 patient with duodenal H had undergone endoscopy and
had reported the occurrence of bloody stool after discharge, which was cured by medical treatment. Fourteen patients had undergone laparoscopic resection, among whom 1 patient with transverse colonic H had undergone laparoscopic resection and complained of occasional abdominal discomfort postoperatively. One patient with a small intestinal H had undergone laparoscopic resection and showed signs of obstruction recurrence, which was relieved after medical treatment. No significant difference was found between endoscopic resection and laparoscopic resection (P > 0.05) ($\chi^2 = 0.373; P = 0.541$).

Follow-up and recurrence. As of 2019-12-29, 3 patients were lost to follow-up, 3 died, and 25 survived. Specifically, 3 patients were lost to follow-up because of the long period; the last visit was used as the end point of follow-up. Of the 3 patients who died, one was treated with laparoscopic surgery for small bowel haemangioma and recovered well. In the second year, he died of underlying diseases, including decompensated liver cirrhosis, primary abdominal bleeding, and hepatorenal syndrome. One of the patients was treated with laparoscopic surgery for small bowel angiomia and recovered well after the operation. Later, the patient died of heart disease and heart failure. Additionally, an 80-year-old elderly patient had received EMR treatment for ascending colon L and recovered well after the operation. The patient died because of intestinal cancer lung metastasis.

No significant difference was found in survival, as determined by the log-rank (Mantel-Cox) test ($\chi^2 = 2.244, P = 0.326$). The survival results for the three pathological types of VTs were consistent. The average follow-up duration among the survivors was 57.06 ± 35.64 months. Except for the 6 who were lost to follow-up and died, the other patients are currently undergoing outpatient follow-up and are still alive. Two people who died had H and one had HL, so the survival rates of the three groups were 100% (8/8) for the HL group, 85.71% (12/14) for the H group, and 88.89% (8/9) for the L group.

Discussion
VTs have a low incidence and are rarely found clinically. Most reports of VTs in the literature have been case reports6–10, with gastrointestinal bleeding as the clinical manifestation. In the present study, an 11-year multicentre retrospective analysis was performed to systematically describe the clinical manifestations, locations, pathological morphology on endoscopy, diagnostic features on imaging, prognosis and survival.

Figure 5. Analysis of various types of gastrointestinal VTs by pathological manifestations. (a) HL, HE × 200; (b) HL, IHC: CD34+/D2-40+. Irregular mucosal hyperplasia was observed in the lamina propria and submucosa. The inner wall was lined with a single layer of flat epithelium, and the cavity contained red blood cells or lymphatic fluid. Immunohistochemistry was positive for CD34 and/or D2-40 expression, suggesting the presence of proliferative vascular and lymphatic vessels; (c) H, HE × 200; (d) H, IHC: CD34+: Clustered vascular hyperplasia in the submucosa of the intestine, lumen irregularity, partial dilation, and positive CD34 expression determined by immunohistochemistry all suggested haemangioma; (e) L, HE × 200; (f) L, IHC: D2-40 + The lymphatic vessels of the lamina propria of the intestinal mucosa showed significant proliferation, and the lumen contained lymphatic fluid. Immunohistochemistry was positive for D2-40 expression.
Previously, diagnosing gastrointestinal H was difficult, and almost all lesions were confirmed during surgery or by inflammation of lymphatic vessels and obstruction of developing lymphatic vessels. Obstruction symptoms appeared only in cases of L, a finding that is also clinically significant and related to the growth pattern of L. L lesions are benign but can cause serious complications, and they may be related to the abnormal development or inflammation of lymphatic vessels and obstruction of developing lymphatic vessels. Obstruction symptoms can lead to symptoms such as abdominal pain, nausea and vomiting. In the present study, 32.26% (10/31) of patients, mainly because of the rapid growth, thin adventitia, and abundant blood supply of VTs. VTs are rare and can easily be missed in the clinic. VTs are often identified clinically because of bleeding or obstruction and are often cleared pathologically after resection. VTs have clear endoscopic and pathological features, and the prognosis with endoscopy and surgery is good. The disease has no invasive manifestations, complications, and can be observed during follow-up endoscopically or surgically, depending on the condition. Studies have shown that endoscopic treatment is suitable for smaller tumours, while laparoscopic/open surgery is recommended for larger tumours. In the present study, 3 patients were not treated and were lost to follow-up, 14 patients had undergone endoscopic resection (EMR/ESD), and 1 patient showed bleeding after EMR and medical treatment. Laparoscopic resection of the lesions was performed routinely in these 14 patients; 3 patients had mild discomfort after laparoscopic resection, which was relieved after symptomatic treatment in all cases. At the same time, 1 case of bleeding was found after biopsy, and the bleeding was stopped after medical treatment. During follow-up, there were no cases of recurrence, and 3 patients died of unrelated causes; survival was good for the three pathological types of VTs, with no significant difference. Therefore, these VTs were noninvasive and did not recur. VTs can be treated if clinical symptoms appear and removed if necessary. Follow-up is recommended when no clinical manifestations occur. Blind biopsy or resection should not be performed because it could lead to unpredictable complications and bleeding.

Conclusion
VTs are rare and can easily be missed in the clinic. VTs are often identified clinically because of bleeding or obstruction and are often cleared pathologically after resection. VTs have clear endoscopic and pathological features, and the prognosis with endoscopy and surgery is good. The disease has no invasive manifestations,
with no tendency for recurrence. Clinical symptoms or conditions can be considered to prevent bleeding and obstruction. In most of these cases, the patient can be recommended for clinical follow-up.

Data availability
The data used to support the findings of this study are available from the corresponding author upon request.

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Competing interests
The authors declare no competing interests.

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