Original Article

CD117, CD34 and DOG-1 Reactivity in Spindle and Epithelioid Cell Tumors of Gastrointestinal Tract

Napaporn Puripat MD[1], Sujitra Tanvanich MSc[1], Kongsak Loharamtaweethong MD[1]

[1] Department of Anatomical Pathology, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand

Objective: To determine the prevalence of CD117, CD34 and DOG-1 reactive in spindle and epithelioid cell tumors of gastrointestinal tract.

Materials and Methods: 82 paraffin blocks of patients from archive of the Department of Anatomical Pathology. Paraffin blocks were searched along with clinical history of gender, age, primary location of the tumor, tumor size, mitotic count and previous pathologic diagnosis. Immunohistochemical studies for CD117, CD34 and DOG-1 were performed. Cases were diagnosed as GIST when ≥2 IHC stainings were positive. Risk assessment of GIST was grouped according to the revised National Institutes of Health [NIH] Risk criteria.

Results: Out of 82 cases, 44 had primarily been diagnosed as GIST whereas the remaining had diagnosis of other mesenchymal tumors. The most frequent positive IHC stainings were DOG-1 and CD117 (56 cases or 68.3%), followed by CD34 (47 cases or 57.3%). Overall, 56 cases (including 44 cases with primary diagnosis of GIST) were diagnosed as GIST by positive staining of 2 or 3 markers. We categorized our patients with GIST into risk groups and found that 28 cases (50.0%) were in the high-risk group.

Conclusion: The present study, all 56 cases of GIST reveals positive CD117 (100%) and DOG-1 (100%). Forty-six out of 56 cases of GIST are also positive CD34 (82.1%). Then CD34 immunohistochemical marker is a supporting marker, using with CD117 or DOG-1 for diagnosis of GIST.

***Keywords*:** Gastrointestinal stromal tumor, CD117, DOG-1, CD34, Gastrointestinal tract, Spindle cell, Epithelioid cell

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Mesenchymal tumors of gastrointestinal tract with spindle- and epithelioid-shaped cells can be found as various benign and malignant tumors, such as, gastrointestinal stromal tumor [GIST], smooth muscle tumors (leiomyoma and leiomyosarcoma), peripheral nerve sheath tumors (schwannoma and malignant peripheral nerve tumor), synovial sarcoma, malignant mesothelioma, sarcomatoid carcinoma. Having similar histomorphology among these tumors, immuno histochemical study has a certain role for making definite diagnosis.

GIST, despite being the most common mesenchymal tumor of the gastrointestinal tract[1], is a rare tumor with a global incidence varied between 10 to 15 cases per million[2]. However, few other studies from North-Norway, Southeast Asia including some areas in china and East Asia (Taiwan) reported 19 to 22 cases per million[2-5].

The most common location of GIST is stomach (56%) followed by small intestine (32%), colo-rectum (6%), and others (6%)[2]. In the past, stromal tumors arising in the gastrointestinal tract were generally regarded as smooth-muscle neoplasms (leiomyoma, leiomyosarcoma, leiomyoblastoma, and bizarre leiomyoma). Until late 1960s that the term 'GIST' was proposed to include any mesenchymal tumors of the gastrointestinal tract: smooth muscle tumors and peripheral nerve sheath tumors e.g. neurofibromas and shcwannomas[6,7]. Later in 1970s when evidences from electron microscopic study and in 1990s from

Correspondence to:
Puripat N. Department of Anatomical Pathology, Faculty of Medicine Vajira hospital, Navamindradhiraj University, Bangkok 10330, Thailand.
Phone: +66-2-2443221, **Mobile:** +66-81-7905674
E-mail: Immy64patho@gmail.com

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immunohistiochemical study revealed negligent portion of smooth muscle components[8-10] but a significant proportion of tumor tissue positive for CD34[11,12]. These CD34 immunopositivity tumor cells raised a possibility that GIST might be related to the interstitial cells of Cajal[13].

In recent years, with the development of effective targeted therapies for GISTs, the prognosis of GISTs patients is significantly improved and an accurate diagnosis of GISTs is important. Several immunohistochemical markers which aid and helpful in diagnosis are CD117 and DOG1 and was found mutation in c-KIT protein (protooncogene) and platelet derivative growth factor receptor (PDGFRA)[7,8,14].

The present study aimed to evaluate the prevalence of GIST in our patients who had mesenchymal tumors with spindle and epithelioid cells who were diagnosed as GIST and non-GIST by studying the expression of CD117, CD34 and DOG-1.

Materials and Methods

The present study was conducted following approval from the institution's ethics committee for research. We identified a list of patients from archive of the Department of Anatomical Pathology who had tumors with diagnoses of GIST, leiomyoma, leiomyosarcoma, fibroma, fibrosarcoma, schwannoma, malignant peripheral nerve sheath tumor, sarcoma or spindle and/or epithelioid cells tumors between January 1, 1990 and June 31, 2017. The primary tumors sites may be from gastrointestinal tract, liver, pancreas, abdomen or omentum. Inclusion criteria were the patients who underwent surgery in the institution, with available clinical data, pathology reports, and paraffin blocks. Patients who did not have any data as well as those who had no available or inadequate tissue for tissue processing were excluded.

All slides were reviewed to select the appropriate blocks for tissue processing by the pathologist (NP). Paraffin blocks were searched from the archive of the Anatomical Pathology Department. Clinico-pathological data collected from the electronic database of the institution and pathological reports included gender, age, primary location of the tumor, tumor size, mitotic count and previous pathologic diagnosis.

Immunohistochemistry was performed using CD117 (c-KIT) (polyclona; Rabbit Anti-Human, DAko, 1: 600), DOG-1 (clone K9, Leica Microsystems, Wetzlar, Germany, 1: 100) and CD34 (Clone QBEan10, DAko, 1: 300). Immunostainings were performed on using the Leica Bond-Max system after antigen retrieval with Bond Epitope Retrieval Solution (Leica Microsystems). Diaminobenzidine was used as a chromogen.

Positive staining, regardless of area or intensity, was interpreted as positive. Melanocytes and mast cells in skin and gastric epithelium were used for positive control of CD117 and DOG-1 respectively whereas positive staining of endothelial cells lining blood vessels or lymphatic channels of appendix was used for positive control of CD34. Diffuse cyctoplasmic staining of CD117 and DOG-1 and cytoplasmic membrane staining of CD34 were interpreted as positive respectively. Cases were diagnosed as GIST when $\geq$2 stainings of CD117, DOG-1, and CD 34 proteins were positive, or else would be diagnosed as other mesenchymal tumors as appropriate. Cases with isolated positive for CD34 was remarked but would not be interpreted as GIST. Risk assessment of GIST was grouped as low, intermediate, and high according to the revised National Institutes of Health [NIH] Risk criteria.

The IHC study for the 3 proteins (CD117, CD34 and DOG-1), including the methods of interpretation and evaluation for the intra- and inter-observer reliability by the 2 pathologists (NP, ST). The results of positive or negative immunostaining were compared between the two authors and between the same authors (at 2 weeks apart) for inter-observer and intra-observer reliability respectively. For any discordant interpretation, the two authors studied the immunostaining slides together for the consensus.

Data were analyzed using SPSS statistical software, version 22.0 (IBM Corp. Armonk, NY, USA). Descriptive data for reactivity of CD117, CD34 and DOG-1 in GISTs, gender, age, locations of the tumors, tumor size and mitotic count were presented as number and percentages. The variables were compared by Chi-square test. All tests were performed at the 2-sided significance level of 5%.

Results

During the study period, one case without pathological and clinical data was excluded. Total of 82 cases met inclusion criteria and were included in the study. Slightly more than half were female (57.0%). Mean age of all patients was 61.72$\pm$15.72 years. Stomach and small bowel were the 2 most common sites of origin, found in 39.0% and 30.0% respectively. Overall tumor size at various locations ranged from less than 1 cm to 28 cm. Characteristic features of the patients and sites of their tumors are shown in Table 1.

The tumors in these patients had pathologic features of spindle cell tumors as demonstrated in Figure 1.

Out of 82 cases, 44 had primarily been diagnosed as GIST whereas the remaining had diagnosis of other mesenchymal tumors (Table 2). Of note, all 44 cases with primary diagnosis GIST had already had positive staining of CD117 and/or DOG-1 and/or CD34. The most frequent positive IHC staining was DOG-1 and CD117 (56 cases or 68.3%), followed by CD34 in 47 cases (57.3%). No cases had isolated positive staining for CD117 or DOG-1. All the three cases (3.7%) with had isolated CD34 stain, diagnosed as hemangiopericytoma, peripheral nerve sheath tumor and spindle cell neoplasm, were negative for CD117 and DOG-1.

Overall, 56 cases (including 44 cases with primary diagnosis of GIST) were diagnosed as GIST by positive staining of 2 or 3 markers (Figure 2).

Of note, 12 cases which had primarily been diagnosed as smooth muscle tumors or spindle cell tumors were re-diagnosed as GIST by immunohistochemical study in this study. All the eight cases with primary diagnoses of Schwannoma, high-grade sarcoma, dermatofibrosarcoma protuberans [DFSP], peripheral nerve sheath tumor and hemangio-

Table 1. Clinical data from e-phis and memory cards

	n (%)	Average tumor size (cm)
Genders		
Male	35 (42.7)	
Female	47 (57.3)	
Locations of the tumors		
Stomach	32 (39.0)	7
Small intestine	25 (30.5)	7
Colon	6 (7.3)	9
Rectum	3 (3.7)	1
Liver	2 (2.4)	0.25
Pancreas	2 (2.4)	5
Esophagus	1 (1.2)	10
Abdomen	6 (7.3)	7
Retroperitoneum	2 (2.4)	11
Omentum	3 (3.7)	-
Total	82	

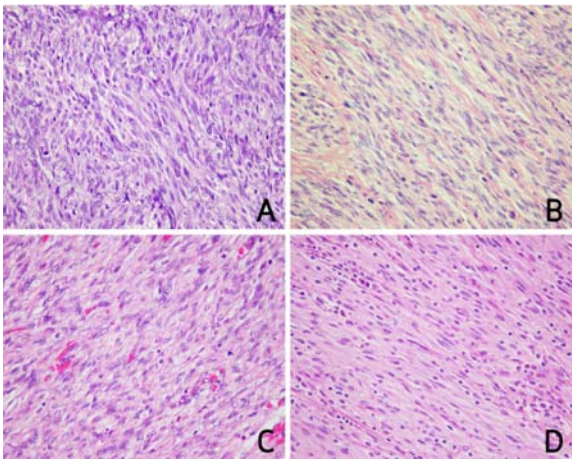

Figure 1. Histomorphology of spindle cell neoplasms. A) Gastrointestinal stromal tumor (Hematoxylin-eosin, ob. X40). B) Leiomyoma (Hematoxylin-eosin, ob. X20). C) Leiomyosarcoma (Hematoxylin-eosin, ob. X40). D) Schwannoma (Hematoxylin-eosin, ob. X40).

Table 2. Previous diagnosis and results of immunohistochemistry CD117, CD34 and DOG-1

Previous diagnosis	Before immunohistochemistry n (%)	After immunohistochemistry		
		CD117 n (%)	CD34 n (%)	DOG-1 n (%)
GIST	44	44 (100.0)	38 (86.4)	44 (100.0)
Leiomyoma	13	4 (30.8)	3 (23.1)	4 (30.8)
Leiomyosarcoma	12	5 (41.7)	3 (25.0)	5 (41.7)
DFSP	1	-	-	-
Schwannoma	3	-	-	-
Peripheral nerve sheath tumor	1	-	-	-
Hemangiopericytoma	1	-	-	-
High-grade sarcoma	2	-	-	-
Spindle cell neoplasm	5	3 (60.0)	3 (60.0)	3 (60.0)
Total	82	56 (68.3)	47 (57.3)	56 68.3)

pericytoma had negative staining of all markers.

Focusing on characteristic features of 56 cases with GIST diagnosis, mean age was 64.18±14.84 years. Female (29 cases, 51.8%) was slightly more common than male with slightly younger age: 65.50±15.14 years in males and 63.00±14.73 years in females ($p = 0.538$). Location and size of tumor as well as their mitotic activities are shown in Table 3. The 2 most common locations of GIST were stomach (48.2%) and small intestine (33.9%). The tumor size ranged from 0.3 to 28.0 cm. Median tumor size was 7.6 cm. The largest tumor size was found in abdomen/ retroperitoneum (median 21.0 cm). More than half (58.2%) of GIST originated from stomach and all from esophagus pancreas and rectum had mitotic figure <5/50 HPF. On the contrary, all GIST of colon and abdomen/ retroperitoneum had mitotic figure >10/50 HPF. The tumor sizes in stomach, small intestine, colon, abdomen and retroperitoneum and esophagus seem to be larger than 5.0 cm in the greatest dimension.

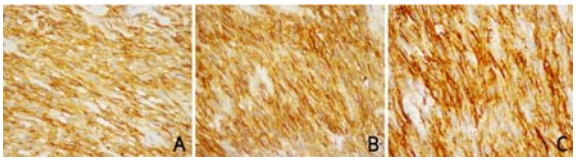

Figure 2. Immunohistochemical studies in gastrointestinal stromal tumor. A) Cytoplasmic expression of CD117 (Immunohistochemistry, ob. X40). B) Cytoplasmic expression of DOG-1 (Immunohistochemistry, ob. X40). C) Cytoplasmic membrane expression of CD34 (Immunohistochemistry, ob. X40).

The authors categorized the patients with GIST into risk groups according to the revised NIH Risk criteria for GIST using locations of the tumor, tumor rupture/intact, and mitotic count to assess the risk of GIST[15] (Table 4), this study found that 28 cases (50.0%)

Table 3. Locations of the tumor, tumor size and mitotic activity

Locations of the tumor (n, %)	n (%)	Median tumor size, cm (range)	Mitotic activity (n, %)		
			≤5/50 HPFs	6 to 10/50 HPFs	>10/50 HPFs
Stomach (28, 50.0%)	25 (50.0)	7.3 (1.0 to 28.0)	19 (70.4%)	5 (18.5%)	3 (11.1%)
Small intestine (19, 33.9%)	19 (33.9)	7.5 (range 0.3 to 19.0)	11 (57.9%)	5 (26.3%)	2 (10.5%)
Colon (2, 3.6%)		8.2 (range 3.4 to 13.0)	-	-	2 (100.0%)
Abdomen and rertoperitoneum (3, 5.6%)		16.3 (range 3.9 to 25.0)	-	-	3 (100.0%)
Esophagus (1, 1.8%)		10.0	1 (100.0%)	-	-
Pancreas (1, 1.8%)		1.6	1 (100.0%)	-	-
Rectum (1, 1.8%)		0.3	1 (100.0%)	-	-
Omentum (1, 1.8%)		-	-	1 (100.0%)	-

Table 4. Joensuu criteria for GIST risk assessment[15]

Risk category	Tumor size (cm)	Mitotic index (per 50HPF)	Primary tumor site
Very low	<2	≤5	Any
Low	2.1 to 5	≤5	Any
Intermediate	2.1 to 5	>5	Gastric
	<5	6-10	Any
	5.1 to 10	≤5	Gastric
High	Any	Any	Tumor rupture
	>10	Any	Any
	Any	>10	Any
	>5	>5	Any
	2.1 to 5	>5	Non-gastric
	5.1 to10	≤5	Non-gastric

were in the high-risk group, 10 cases (18.0%) in the low risk, and 16 cases were in the low or intermediate risk groups (8 cases or 15.0% each). The present study assessed the risk according to the sites of tumors (Table 5) and found that GIST of non-gastric sites had the highest proportion of having high risk GIST. On the other hand, GIST of stomach had the highest proportion of low risk GIST.

Discussion

Spindle and epithelioid mesenchymal tumors of gastrointestinal tract and abdomen may be seen in diverse types of tumors. Hence, a definite diagnosis from hematoxylin-eosin staining can hardly be made. IHC which has affordable cost is commonly used nowadays to aid in diagnosis any lesions/ tumors with uncertain or equivocal diagnosis from hematoxylin-eosin staining. The special investigation is especially important when the diagnosis has impact on the type of treatment.

GIST is uncommon tumors being found less than 1% yet[15], it is most common among mesenchymal tumors of the gastrointestinal tract[14]. The most common location of GIST is stomach (60 to 70%) and the other organs are small intestine (20 to 30%), large intestine and rectum (5%), esophagus (less than 5%), and omentum/ mesentery (rare)[7,16,17]. The present study found 68% of GIST among all mesenchymal tumors identified in our institution with stomach (48%) and small intestine (34%) as the 2 most common locations. The other sites are abdomen and retroperitoneum (5.6%), colon (3.6%). Esophagus, pancreas, rectum and omentum are rarely found (1.8%) Mean age of our GIST patients was 64 years which was in the range of 55 years to 65 years[1,18]. The present study, mean age was 64.4 years with Male (65.5 years) a bit older than female (63.1 years) and was found in female (51.8%) slightly more than male (48.2%).

Having similar histomorphology, GIST must be differentiated from other mesenchymal tumors. Few immunohistochemical markers are currently used for a diagnosis of GIST. A gene product KIT (CD117) of c-Kit and a mutant c-Kit or PDGFRA induced tumor are specific markers which aid in diagnosis of GIST[19,20]. However, these 2 tests are not available in most laboratories. CD34 which has long been used is now considered as a supportive marker along with other more definite markers because it was quite non-specific[19] and had a wide range of immunohisto chemical reactivity of 40 to 82%[6,7,19,21-26]. Two other markers which were also used are CD117 and DOG-1. Many reports show positive CD117 in 65 to 100% of GIST[19,22,27-38] and positive DOG-1 in 75 to 99% of GIST[19,27-33]. However, up to 35% of GIST may have negative CD117 staining, so another immunohisto chemical marker of DOG-1 is helpful in CD117-negative mesenchymal tumors[39,40]. The present study, all 56 cases of GIST reveals positive CD117 (100%) and DOG-1 (100%). Forty-six out of 56 cases of GIST are also positive CD34 (82.1%). While all eight cases of schwannoma, pleomorphic undifferentiated sarcoma, DSFP, peripheral nerve sheath tumor and hemangio pericytoma are negative for CD117 and DOG-1. Two cases of DSFP and hemangiopericytoma are positive CD34.

Immunohistochemical markers for CD117 and DOG-1 are useful immunohistochemical markers for diagnosis of GIST and less positive in the other spindle mesenchymal tumors. From this study, both CD117 and DOG-1 are positive in all cases of GIST (100%) and using one of them, CD117 or DOG-1 with additional markers (SMA, desmin, S-100 eta) can make diagnosis

Table 5. Risk stratification of GIST

Locations of the tumor (n)	Very low n (%)	Low n (%)	Intermediate n (%)	High n (%)
Stomach (28)	4 (14.3%)	7 (25.0%)	7 (25.0%)	9 (32.1%)
Small intestine (19)	2 (10.5%)	3 (15.8%)	1 (5.3%)	11 (57.9%)
Colon (2)	-	-	-	2 (100.0%)
Esophagus (1)	-	-	-	1 (100.0%)
Pancreas (1)	1 (100.0%)	-	-	-
Abdomen and retroperitoneum (3)	-	-	-	3 (100.0%)
Rectum (1)	1 (100.0%)	-	-	-
Omentum (1)	-	-	-	1 (100.0%)
Total (56)	8 (14.3%)	10 (17.9%)	8 (14.3%)	28 (50.0%)

of GIST. While positive CD34 alone cannot make diagnosis of GIST because there are the other mesenchymal spindle cell tumors can express CD34. So immunohistochemical marker for CD34 is supporting marker, using with CD117 or DOG-1 for diagnosis of GIST.

GISTs have variety of malignant potential from benign to aggressive sarcoma[15]. Base on revised NIH Risk criteria, there were four parameters using tumor size, mitotic count, locations of the tumor and tumor rupture[15].

The malignant potential of GISTs varies from virtually benign tumors to aggressive sarcomas[15]. Patient prognosis was commonly stratified based on tumor size, mitotic count, locations of the tumor and tumor rupture[15]. The present study, based on only tumor size and mitotic activity, found high-risk GIST was most commonly in non-gastric sites (Table 5). It showed that non-gastric GISTs trended to have more malignant behavior compared to gastric GISTs. However, capsule rupture was not included in the present study and limited for evaluation of true risk assessment in the present study.

In conclusion, Immunohistochemical studies for CD117 and DOG-1 have an important role to make definite diagnosis of GISTs among spindle and/or epithelioid tumors in gastrointestinal tract and abdomen. This was evidenced that 14.6% had a revised diagnosis from leiomyoma, leiomyosarcoma and spindle cell neoplasm to GIST. This should be critical in selecting an appropriate type of adjuvant treatment.

What is already known on this topic?

Immunohistochemistry plays an important role in diagnosis of GIST because its histomorphology can mimic various mesenchymal tumors of gastrointestinal tract. CD34, CD117 and DOG-1 are recently used to diagnose GIST. CD117 and DOG-1 are mostly positive in GIST and less than 5% are negative. CD34 is used as supportive marker because CD34 alone and can express in various mesenchymal tumor. Combination of CD117, DOG-1 and CD34, it can make diagnosis of GIST in practical work.

What this study adds?

Expression of CD117 and DOG-1 were found in the high percentage (100%) and less expression in CD34 (82.1%). In practical, CD117 or DOG-1 can be used as adjunct marker CD34 in diagnose of GIST to reduce cost in performing immunohistochemistry.

Potential conflicts of interest

The authors declare no conflict of interest.

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