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Histopathologic and Immunohistochemical Analysis of 66 Cases of Gastrointestinal Stromal Tumor

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Abstract

Background and Objective: To investigate the histopathological characteristics and immunohistochemistry of gastrointestinal stromal tumors (GIST). Immunohistochemistry (IHC) refers to the expression and meaning of CD117, DOG-1, CD34. Methods: Sixty-six gastrointestinal stromal tumor (GIST) samples with complete clinical data and definite clinicopathological diagnosis were collected from the Seventh Affiliated Hospital of Sun Yat-sen University from January 2019 to December 2022. Retrospective analysis was performed on the pathological data of 66 patients with GIST, and the histopathology and IHC were analyzed and summarized. Results: Among the 66 cases, 46, 14, 1, 5 were found in the stomach, small intestine, large intestine, and gastroenteral area. There were 45 cases (97%), 11 cases (79%), 1 case (100%), 5 cases (100%) in order of fusiform cell type. There were 1 case (3%), 2 cases (14%), 0 case, 0 case of upper dermatiform; Mixed type in 0 case, 1 case (7%), 0 case, 0 case; CD117 positive 66 cases (100%), DOG-1 positive 66 cases (100%), CD34 positive 61 cases (92%), CD117 and/or CD34 negative 5 cases (8%); CD34, CD117 and DOG-1 were negative simultaneously in 0 case. 19 cases (28%) were positive for SMA and 7 cases (11%) were positive for S-100. Conclusion: Fusiform cell type is the common type of GIST, followed by epithelioid type and mixed type, but the tumor sites are different, and the comparison cases are not completely the same. CD117, DOG-1 and CD34 are high surface in GIST, and the combination of SMA, S-100 and histomorphology can be used to diagnose most GIST.

Keywords

Gastrointestinal Stromal Tumor, Immunological Organization, CD117, DOG-1, CD34

1. Introduction

Gastrointestinal stromal tumors (GIST) are the most common tumors of gastrointestinal tract, accounting for about 70% of gastrointestinal tumors. In the past, due to the limitation of the disease conditions, there was a big difference in the understanding of its diagnosis, so that the most commonly diagnosed gastroenteric smooth myoma or schwannoma belongs to GIST [1]. With the emergence of immunohistochemistry (IHC), molecular pathology and the gene molecular target drug Gleevec, GIST has become a hot spot for research. In this paper, retrospective analysis of 66 patients with GIST was conducted to investigate the clinical pathological features and the expression and significance of IHC.

2. Materials

Sixty-six gastrointestinal stromal tumor (GIST) samples with complete clinical data and definite clinicopathological diagnosis were collected from the Seventh Affiliated Hospital of Sun Yat-sen University from January 2019 to December 2022. The patients ranged in age from 41 to 85 years, with an average age of 63 years.

3. Methods

3.1. Histological Methods

All specimens were fixed by 10% neutral formalin, embedded in regular sphalerite wax, sliced 4 μm, hematoxylin-eosin (HE) hematoxylin-Eosin (HE), and observed by light microscope. Two experienced pathologists were rediagnosed and classified (spindle-cell, epithelioid, mixed) based on microscopic histomorphology, according to the national institutes of health（NIH) for risk classification.

3.2. IHC Staining

IHC primary antibodies CD117, DOG-1, CD34, SMA and S-100 were all use antibodies, and primary antibodies and secondary antibodies were purchased from Guangzhou Ambiping Company. IHC staining was performed by streptavidin-perosidase (SP) method, strictly in accordance with the instructions. Positive counterpart was set for each batch of dyeing, and primary antibody was replaced by phosphate buffer saline (PBS) for negative counterpart.

3.3. Statistical Processing

All data were processed by Microsoft Excel 2021 software and descriptive statistics were adopted.

4. Result

4.1. Clinicopathological Results

There were 35 male patients and 31 female patients; 47 cases were older than 50 g and 19 cases were younger than 50 g. The lesions were in the stomach in 46

cases, in the intestine in 15 cases, and in the parenteral in 5 cases. There were 44 cases of very low risk, 11 cases of low risk, 55 cases of very low risk and low risk, and 11 cases of medium and high risk. There were 44 cases with tumor diameter less than or equal to 2 cm, 12 cases with tumor diameter about 2 cm less than or equal to 5 cm, a total of 56 cases, and a total of 10 cases larger than 5 cm, as shown in Table 1.

4.2. Histological Results

In this group of 66 GIST patients, there were 62 fusiform cell types (93%), 3 cuticular types (5%) and 1 mixed type (2%), as shown in Table 2.

4.3. IHC Results

In this group, 61 cases (92%) were positive for CD117 and CD34, and 66 cases (100%) were positive for CD117 and/or DOG-1, and both CD117 and Dog-1 were expressed in diffuse positivity. There were 7 (11%) S-100 positive cases and 19 (28%) SMA positive cases, all of which were focal tumor expression, as shown in Table 3.

5. Discussion

GIST is a mesenchymal tumor of the gastrointestinal tract [1], which is of great clinical significance, with an annual incidence of about 11 - 18 cases per million people worldwide [2] [3]. In the earlier literature, researchers suggested that these tumors resembled normal smooth muscle cells and contained "myofibril", leading to the misclassification of them as various smooth muscle tumors, such as leiomyoma, leiomyosarcoma, and "smooth muscle blastoma". It is now believed to be an independent origin between the gastrointestinal Cajal interstitial cells of cajal (ICC), or ICC-differentiated tumors [4] [5], which are the most common mesenchymal sources in the gastrointestinal tract Sexual neoplasm.

GIST can occur at any age, mostly in middle age, with no significant gender difference. Tumors can be located in any part of the digestive tract, with the stomach being the most common site (60%), followed by the small intestine (30%) and, to a lesser extent, the colon and esophagus. Some primary tumors occur in the mesenteric fat and greater omentum, with no apparent attachment to the intestinal wall. This condition may be that the tumor is primarily located in the serous membrane or subserous membrane initially and separates from the intestinal wall over time. Extremely rare cases of extra-gastrointestinal GIST, especially in the lung and female genital tract, are collectively referred to as extra-gastrointestinal GIST. Specific symptoms depend on the location of the tumor. Patients may have gastrointestinal bleeding due to mucosal ulcers, obstruction such as abdominal pain or vomiting due to gastric outlet obstruction, and less often present as a palpable mass. Tumors are usually discovered by chance through surgery with endoscopy, radiographic imaging, or other unrelated indications.

Table 1. GIST results of clinical pathology [*n* (%)].

Clinicopathologic feature	N
Gender	
Male	35 (53)
Female	31 (47)
Age (g)	
≤50	19 (29)
>50	47 (71)
Tumor size (cm)	
≤2	44 (67)
V2 and ≤ 5	12 (18)
V5 and ≤ 10	6 (9)
V10	4 (6)
The risk of Gist	
very low	44 (67)
low	11 (17)
intermediate	3 (4)
high	8 (12)
location	
stomach	46 (69)
small intestine	14 (21)
Large intestine	1 (2)
extra-gastrointestinal stroma	5 (8)

Table 2. Various types of GIST in stomach, small intestine，large intestine and parenteral [*n* (%)].

Location Histological types	Stomach	Small intestine	Large intestine	extra-gastrointestinal
Spindle cell type	45 (97)	11 (79)	1 (100)	5 (100)
Epithelial cell type	1 (3)	2 (14)	0 (0)	0 (0)
Mixed cell type	0 (0)	1 (7)	0 (0)	0 (0)

Table 3. Expression of immunohistochemical methods (CD117, DOG-1, CD34, SMA, S-100) in 50 cases of GIST [n(%)].

IHC	(+)	(-)
CD117	66 (100)	0 (0)
DOG-1	66 (100)	0 (0)
CD34	61 (92)	5 (8)
SMA	19 (28)	47 (72)
S-100	7 (11)	59 (89)

Disease transmission is typically characterized by liver metastasis and/or peritoneal surface spread. Lymph node metastasis is very rare, but when it does occur, it is associated with succinate dehydrogenase (SDH) deficient GIST, which differs clinicopathologically and molecularly from the common GIST. Pediatric GIST accounts for less than 2% of all the cases, mostly in women, accounting for the majority of SDH defective GIST. Clinical neoplastic syndromes associated with GIST include Carney triad, Carney-Stratakis syndrome, and neurofibromatosis type I. GIST ranges in size from < 1 cm (the so-called micro-GIST) to the largest 40 cm. The median size of gastric GIST is 6 cm, duodenum is 4.5 cm, and jejunum and ileum are 7 cm. GIST is usually located in submucosal, muscularis proper or subserous masses in the gastrointestinal wall, and it is common for serous swelling and mucosal ulcers. The section is usually well-delimited fishy, fibrous, or gelatinous, often accompanied by central cystic changes and bleeding, and apparent necrosis is rare.

Gist has relatively limited histological features. Most boundaries are clear, but some exhibit invasive edges. GIST tumor cells mainly have two forms, spindle cells and epithelioid cells, which can be divided into spindle cell type, epithelioid type and mixed type according to histological characteristics. Spindle cell type is the most common about 70%, epithelioid type 20%, mixed type is rare. Microscopically, the cells of spindle tumor are often arranged in the form of cross bundles, palisades, swirls, and perinuclear vacuoles, which are difficult to distinguish from smooth muscle tumors, fibrohistiocytogenic tumors, and neurogenic tumors. Epithelioid tumor cells are diffuse, nestlike, with deep eosinophilic, bright or vacuolar cytoplasm, and varied nuclei, sometimes indistinguishable from atypical leiomyoma and sigma-ring tumor cells. In this group, spindle cell type was 93%, epithelioid type was 5%, and mixed type was 2%. In 66 cases, the proportion of spindle-cell type in stomach, small intestine, large intestine and outside intestine was 97%, 79%, 100% and 100%, respectively. Epithelioid type accounted for 3%, 14%, 0% and 0%, respectively. Mixed type accounted for 0%, 1%, 0% and 0% respectively. Spindle cell type was the most common, epithelioid type was the second, mixed type was rare, but the proportion of different types was not exactly the same in different sites. The clinical/biological behavior of Gist ranges from "no risk" to "high risk" clinically aggressive tumors with widespread spread [6]. Most gists have low mitotic activity. Risk stratification was assessed by counting the amount of mitosis in a 5 mm^2 area, and the number of high magnification fields was correlated with the microscope used. Based on data from two large studies, mitotic counts were combined with the primary tumor site and tumor size to determine the risk of disease progression [6] [7].

GIST has its unique genetic changes, the most important of which is c-Kit proto-oncogene mutation. CD117 is the egg white product of c-Kit, and almost all GIST has c-Kit surface, with a positive rate of 94% - 98% [8]. Kit protein is strongly expressed in 95% of Gist with diffuse cytoplasmic staining, or a few are membranous or Golgi para-dot positive. About 5% of KIT-negative Gist occur mostly in the stomach and are epithelioid cell types, with 70% of these tumors

having PDGFRA mutations. The remaining 30% of KIT-negative Gist are almost always the "wild type". Kit mutant Gist lacking kit protein expression is rare. About 5% of Gist have nodular protein expression, usually focal or scattered positive (usually gastric epithelioid Gist), and < 1% of Gist have focal positive cytokeratin expression. Diffuse Kit protein expression is not common in other tumor types and therefore facilitates the diagnosis of Gist. CD34 is the original plasmogenic cytoplasmic antigenic GIST, which has a high surface reach rate of 70% - 80% [9]. Most scholars believe that the combination of CD117 and CD34 should be an effective way to diagnose GIST. In this group, 94% of CD117 was positive and 80% of CD34 was positive. Some GISTCD117 and/or CD34 were negative. In this test group, 12 cases (24%) were negative. This article also reported that 4% - 15% of GIST cases were negative or unclear on CD117 [10], which caused confusion in the diagnosis of GIST. DOG-1 is a newly discovered antibody marker specifically expressed in GIST, which is a membrane penetrating protein on human 11q13 chromaticity. It is positively expressed in gastrointestinal stromal tumor cells, but not in other tissues, with a positive rate of 94% - 96% [11] [12] [13]. DOG1 is a chloride channel protein, and its overexpression is detected by Gist gene expression profile compared with other stromal tumors. More than 95% of Gist showed Dog-1 diffuse cytoplasmic and membrane expression. Dog-1 can be used in the diagnosis of KIT-negative Gist because it is expressed in most of these tumors. Diagnosis of challenging Gist with both Dog-1 and KIT-negative cases is rare (2.6%), so the lack of expression of these two markers requires further gene mutation detection to confirm the diagnosis. An important subset of Gist with both Dog-1 and KIT-negative cases may be Kit or PDGFRA mutations. Dog-1 is rarely expressed in other stromal tumors. Focal expression of Dog-1 has been reported in a few leiomyosarcomas, retroperitoneal uterine leiomyomyomas, synovial sarcomas, and PEComas. In this study, the positive rate of DOG-1 was 100%, which was similar to that of the reported results.CD34 was negative in 5 cases (8%), and CD117 and DOG-1 combined with CD34 had a higher positive rate in GIST.

Studies have shown that myogenic and neurogenic immune markers are low expressed in GIST, with a positive rate of SMA about 25% and S-100 23.7% [14]. In this study, the positive rate of SMA was 28% and that of S-100 was 11%. The positive rate of S-100 was slightly lower than the data reported in the literature, which may be due to the different interpretation standards of the positive rate due to the use of antibody models. According to electron microscopy, some GIST tumor cells have the characteristics of autonomous nerve and smooth muscle, which may be because the tumor originated from Cajal mesenchymal cells, which are widely distributed between the ring and longitudinal myofilms, close to the gastrointestinal intermuscular plexus, and closely connected with gastrointestinal motor neurons and smooth muscle cells. Cajal cells originate from the same precursor stem cells as smooth muscle [4] [5]. Positive SMA and S-100 may indicate that tumor cells differentiate into smooth muscle or nerves. In pathological diagnosis of GIST, the combination of CD117, DOG-1, CD34, SMA and

S-100IHC staining and histological features is recommended for diagnosis and differential diagnosis.

At present, most basic units in China do not have the conditions for molecular detection. In practice, pathological diagnosis of GIST mainly relies on histological observation and IHC detection. This retrospective study found that CD117, DOG-1 and CD34 had a high positive rate in GIST, and the combination of SMA and S-100 could make a definite diagnosis for most GIST. For cases considered to be GIST by morphology but negative for CD117 and/or DOG-1 and/or CD34, especially for CD117, molecular pathologic tests should be performed if necessary, after excluding other types of tumors. As a retrospective study, this study has its inherent limitations. The small sample size may lead to some bias in the results.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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