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Immunohistochemical Patterns in Gastrointestinal Stromal Tumors with Clinicopathologic Correlation

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Abstract
Background: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract and are believed to arise from the interstitial cells of Cajal. They exhibit diverse clinical, morphological, and immunohistochemical features. Immunohistochemistry (IHC), particularly C-kit (CD117) and DOG1 expression, plays a pivotal role in establishing the diagnosis and differentiating GISTs from other mesenchymal tumors. The present study aimed to evaluate the immunohistochemical patterns of GISTs and correlate them with their clinicopathological characteristics.
Methods: This retrospective case series included 10 histopathologically diagnosed GIST cases over a 9-year period, comprising 5 excision biopsies and 5 tru-cut biopsies. Clinical details including age, sex, tumor site, size, and metastatic status were obtained from patient records. Histopathological evaluation was performed on hematoxylin and eosin-stained sections for tumor morphology, mitotic activity, necrosis, and risk assessment. Immunohistochemical markers assessed included C-kit, DOG1, CD34, SMA, Desmin, S100, SDHB, and other ancillary markers as indicated.
Results: Patients ranged from 44 to 84 years of age (mean age: 64.0 years) with a marked male predominance (9:1). The stomach and duodenum were the most common sites (30% each). Spindle-cell morphology was observed in 8 (80%) cases, while 2 (20%) cases showed epithelioid morphology. Tumor size ranged from 5.5 to 13 cm. Among resected tumors, necrosis was absent and most cases demonstrated low mitotic activity. All cases showed positivity for C-kit and DOG1 (100%), while CD34 positivity was observed in 60% of cases. SMA and SDHB exhibited variable expression. Negative staining for Desmin, S100, cytokeratins, EMA, and other lineage-specific markers helped exclude histological mimics.
Conclusion: Combined histomorphological evaluation and immunohistochemical profiling are essential for the accurate diagnosis of GIST. Universal expression of C-kit and DOG1 highlights their diagnostic utility, while ancillary markers aid in differential diagnosis and clinicopathological characterization.
Key Word: GIST, IHC, C-kit, DOG-1

I. INTRODUCTION:

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract and are believed to arise from the interstitial cells of Cajal.[1] They occur most frequently in the stomach, followed by the small intestine, and exhibit variable clinical behavior depending on tumor size, mitotic activity, and anatomical location.[2]

Histologically, GISTs may show spindle cell, epithelioid, or mixed morphology, often overlapping with other mesenchymal tumors. Immunohistochemistry plays a crucial role in diagnosis, with KIT (CD117) and DOG1 serving as the most sensitive and specific markers.[3] The identification of KIT and PDGFRA mutations has further enhanced diagnostic accuracy and enabled targeted therapy with tyrosine kinase inhibitors.[4]

The present study was undertaken to evaluate the immunohistochemical patterns of GISTs and correlate them with their clinicopathological features.

II. CASE SERIES:

A total of 10 cases of GISTs were reported during the 9-year study period. All cases with a confirmed diagnosis of GIST based on histopathology and IHC were included. Specimens consisted of tru-cut biopsies and excision specimens. Hematoxylin–eosin stained slides were reviewed for architectural pattern, cytomorphology, mitotic index, stromal features, and necrosis. IHC panels included CD117, DOG1, CD34, SMA, desmin, and S100. Clinical data including tumor size, location, and treatment were obtained from patient records.

Table 1. Demographic and Clinicopathological Characteristics of GIST Patients (N = 10)

Case No.	Age (Years)	Sex	Tumour Site	Histological Type	Tumour Size (cm)	Mitotic Activity	Necrosis	Risk Category
1	44	Female	Ileum	Spindle cell	10 × 8 × 5.5	1/5 HPF	Absent	High risk
2	72	Male	Duodenum	Spindle cell	5.5 × 4 × 3.5	≤5/5 HPF	Absent	Not available
3	62	Male	Jejunum	Spindle cell	7 × 5.2 × 3.5	Scanty mitoses	Absent	Low risk
4	54	Male	Stomach	Spindle cell	13 × 11 × 9	>5/50 HPF	Absent	High risk
5	75	Male	Duodenojejunal flexure	Spindle cell	11.5 × 10 × 6	3/50 HPF	Absent	High risk
6	84	Male	Duodenum	Spindle cell	NA	NA	NA	NA
7	51	Male	Stomach	Spindle cell	10 × 7.9	NA	NA	NA
8	53	Male	Stomach	Epithelioid	NA	NA	NA	NA
9	75	Male	Duodenum	Spindle cell	6.5 × 6.1 × 8.1	NA	NA	NA
10	70	Male	Ileum	Epithelioid	13 × 7.4 × 8.2	NA	NA	NA

A total of 10 patients with gastrointestinal stromal tumors (GISTs) were included in the study. The age of the patients ranged from 44 to 84 years, with a mean age of 64.0 ± 13.1 years. There was a marked male predominance, with 9 (90.0%) males and 1 (10.0%) female.

The most common tumor sites were the duodenum and stomach, each accounting for 3 (30.0%) cases, followed by the ileum in 2 (20.0%) cases. The jejunum and duodenojejunal flexure accounted for 1 (10.0%) case each.

Histologically, spindle cell morphology was the predominant subtype, observed in 8 (80.0%) cases, whereas epithelioid morphology was identified in 2 (20.0%) cases.

Among the five resected specimens, tumor size ranged from 5.5 cm to 13 cm. Necrosis was absent in all resected tumors. Risk stratification was available for four cases, of which three (75.0%) were categorized as high risk and one (25.0%) as low risk. Mitotic activity varied from scanty mitoses to more than 5 mitoses per 50 high-power fields

Table 2. Immunohistochemical Profile of GIST Patients (N = 10)

Case No.	Positive Markers	Negative Markers
1	C-Kit, DOG1, CD34, SMA	S100, Desmin
2	C-Kit, DOG1, CD34, SDH	Not available
3	DOG1, C-Kit	Pancytokeratin, CK8/18, SMA, CD34, Desmin, S100, EMA
4	C-Kit, DOG1, CD34, SMA	S100, MDM2, Desmin, SDHB
5	C-Kit, DOG1, CD34	Desmin, S100
6	C-Kit, DOG1	Cytokeratin, CK8/18, CK7, CK20, LCA, CD30, S100, HMB45
7	CD117, DOG1, CD34, SDH-B	Not available
8	C-Kit, DOG1, SDHB, Synaptophysin (weak)	Cytokeratin, EMA, Chromogranin-A, LCA, CD43, SOX10
9	C-Kit, DOG1, CD34	SMA, Desmin, S100
10	C-Kit, DOG1, SDHB	S100, CD34, HSA, Arginase, EMA

Table 3. Frequency of Immunohistochemical Marker Expression in GIST Patients (N = 10)

Marker	Positive Cases, n (%)
DOG1	10 (100.0)
C-Kit/CD117	10 (100.0)
CD34	6 (60.0)
SDHB	4 (40.0)
SMA	2 (20.0)
Synaptophysin (weak)	1 (10.0)

Immunohistochemical analysis revealed positivity for DOG1 and C-Kit/CD117 in all 10 (100.0%) cases, confirming the diagnosis of GIST. CD34 expression was observed in 6 (60.0%) cases, while SDHB positivity was noted in 4 (40.0%) cases. SMA positivity was identified in 2 (20.0%) cases. One epithelioid GIST demonstrated weak Synaptophysin positivity. Markers used to exclude histological mimics, including Desmin, S100, cytokeratins, EMA, Chromogranin-A, LCA, SOX10, HMB45, HSA, and Arginase, were negative in the

respective cases tested. Overall, the tumors exhibited a characteristic immunophenotype with universal DOG1 and C-Kit expression and variable CD34 and SDHB positivity.

III. Discussion

Table 4. Comparison of Clinicopathological and Immunohistochemical Features of GISTs in the Present Study and Previous Studies

Parameter	Devi J et al. (n=5)	Varshney et al. (n=92)	Present Study (n=5)
Mean age (years)	43.6	49.0	61.4
Male : Female	2:3	60:32	4:1
GI tract tumors	5 (100%)	76	5 (100%)
Size >10 cm	3 (60%)	34 (37.0%)	3 (60%)
Spindle cell type	2 (40%)	69 (75.0%)	5 (100%)
High-grade tumors	3 (60%)	54	1 (20%)
Mitotic count >5/50 HPF	2 (40%)	30 (32.6%)	1 (20%)
Necrosis present	2 (40%)	37 (40.2%)	0
C-Kit positivity	4 (80%)	91 (98.9%)	5 (100%)
DOG1 positivity	Not reported	64	5 (100%)
CD34 positivity	Not reported	87	4 (80%)

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract and exhibit considerable clinicopathological and molecular heterogeneity.[1,2] In the present case series, patients ranged in age from 44 to 84 years, with a mean age of 64.0 years and a marked male predominance (male ratio, 9:1). These findings are comparable to previous studies, although the mean age in our series was higher than that reported by Devi J et al. and Varshney et al.[3,4]

The duodenum and stomach were the most common tumor sites in the present study, accounting for 30% of cases each. Histologically, spindle cell morphology predominated, being observed in 80% of cases, while epithelioid morphology was identified in 20%. These findings are consistent with previous reports demonstrating spindle cell morphology as the predominant histological subtype of GIST.[1,2]

Among the resected tumors, lesion size ranged from 5.5 cm to 13 cm, with the majority measuring more than 10 cm. Risk stratification demonstrated that most evaluable cases belonged to the high-risk category. Mitotic activity varied from scanty mitoses to more than 5 mitoses per 50 high-power fields, reflecting the biological heterogeneity of GISTs. Tumor size, mitotic count, and anatomical location remain the most important prognostic parameters in currently accepted risk-stratification systems.[5]

Immunohistochemistry played a pivotal role in establishing the diagnosis, particularly in tru-cut biopsy specimens where tissue architecture was limited. All cases demonstrated positivity for C-Kit (CD117) and DOG1, confirming the diagnosis of GIST. CD34 positivity was observed in 60% of cases, while SMA expression was identified in a minority of tumors. Markers such as Desmin, S100, cytokeratin, EMA, and other lineage-specific markers were consistently negative in the tested cases, aiding in the exclusion of histological mimics including smooth muscle tumors, schwannomas, metastatic carcinomas, and neuroendocrine neoplasms.[1,6]

The universal expression of DOG1 and C-Kit in our series highlights their value as highly sensitive diagnostic markers for GIST. DOG1 is particularly useful in tumors with unusual morphology and in limited biopsy material and is therefore recommended as part of the routine immunohistochemical panel for suspected GISTs.[6,7] The combination of morphology and immunohistochemistry enabled accurate classification of both spindle cell and epithelioid variants.

Molecular alterations involving KIT and PDGFRA are known to drive the pathogenesis of most GISTs and have important therapeutic implications. Approximately 85–90% of GISTs harbor KIT mutations, while 5–10% demonstrate PDGFRA mutations. A smaller subset lacks mutations in either gene and is categorized as wild-type GIST.[1,8] Although molecular testing was not available for all cases in the present series, the consistent expression of C-Kit and DOG1 supports the underlying role of KIT/PDGFRA pathway activation. Identification of these molecular alterations is clinically relevant because it predicts response to tyrosine kinase inhibitors and contributes to risk assessment and patient management.[8]

The present case series emphasizes the importance of integrating clinical findings, histomorphology, and immunohistochemistry for the accurate diagnosis of GIST. While excision specimens allow comprehensive assessment of tumor size, mitotic activity, and risk stratification, tru-cut biopsies rely heavily on immunohistochemical confirmation. The characteristic expression of C-Kit and DOG1, together with the

exclusion of differential diagnoses through ancillary markers, remains the cornerstone of GIST diagnosis and facilitates appropriate therapeutic decision-making. [1,6]

IV. Conclusion

Immunohistochemistry (IHC) remains an essential tool for the diagnosis, classification, and prognostication of gastrointestinal stromal tumors (GIST). Both tru-cut and excision biopsy specimens benefit from IHC, with markers such as C-kit (CD117) and DOG1 reliably confirming the diagnosis, while additional markers like CD34, SMA, S-100, and Ki-67 provide important insights into tumor morphology, proliferative activity, and risk stratification. In limited tru-cut biopsies, IHC ensures accurate early diagnosis and aids in therapeutic decision-making, whereas excision biopsies allow comprehensive evaluation of tumor heterogeneity and immunophenotypic profiles, guiding precise prognostic assessment and potential molecular testing. Clinicopathologic correlation demonstrates that spindle-cell and epithelioid morphologies, tumor size, mitotic index, and necrosis, when combined with IHC findings, are crucial for predicting tumor behavior and determining patient management. Overall, the integration of IHC patterns with clinicopathologic parameters enhances diagnostic accuracy, informs targeted therapy, and contributes to improved clinical outcomes in patients with GIST.

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