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The Transfigured Ingot-Gastrointestinal Stromal Tumour

Mini Review

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Gastrointestinal stromal tumour is a frequently discerned, mesenchymal neoplasm occurring within gastrointestinal tract. Predominantly incriminating gastric region, tumefaction arises from interstitial cells of Cajal which constitute myenteric plexus situated within muscularis propria. Previously designated as gastrointestinal smooth muscle tumour, gastrointestinal autonomic nerve tumour, leiomyoblastoma, smooth muscle tumour of uncertain malignant potential or gastrointestinal pacemaker cell tumour, gastrointestinal stromal tumour may exhibit malignant biological behaviour [1,2]. Of obscure aetiology, majority of neoplasms are sporadic. However, few familial neoplasms may occur. Chromosomal mutations of KIT and PDGFRA genes are singularly associated with the tumour. Neoplasm may be discovered incidentally during various imaging or endoscopic procedures of gastrointestinal tract [1,2].

Tumefaction preponderantly incriminates tubular gastrointestinal tract and occurs in decreasing order of frequency within stomach, jejunum, ileum, duodenum, rectum, colon, appendix or oesophagus(1,2). Gastric neoplasms are frequently malignant, in contrast to tumours occurring within small intestine wherein prognostic outcomes are contingent to tumour magnitude, proportionate mitosis and location of tumour initiation [1,2]

Extra-gastrointestinal stromal tumour is configured of extraneous stromal neoplasms arising from omentum, mesentery, retroperitoneum or pleura. Additionally designated as micro or mini neoplasm, subclinical gastrointestinal stromal tumour appears as a miniature tumefaction comprised of interstitial cells of Cajal or accumulated gastrointestinal stromal tumour-like cells with ~10 millimetre magnitude [1,2].

Tumefaction commonly arises within elderly subjects with mean age of tumour discernment at ~ 65 years. An equivalent gender predilection is observed [1,2]. Majority (~75%) of tumefaction are associated with activating genetic mutation of proto-oncogene KIT confined to exon 11. Besides, mutations within platelet derived growth factor receptor-α (PDGFR-α) may appear. Subsequently, constitutive phosphorylation of receptor tyrosine kinase and activation of downstream pathways is exemplified with consequent cellular proliferation and survival [1,2].

The neoplasm is associated with certain contemporary genetic mutations of NF1 gene or mutations within RAS/RAF/MEK pathway, as expounded with ETV1 transcription factor associated gastrointestinal stromal tumour [1,2].

Genomic mutation of succinate dehydrogenase subunits, commonly SDHA, initiates accumulation of succinate or enhanced transcription of HIF1α-regulated genes and decimated DNA methylation. Absent immune expression of subunit SDHB may occur [1,2].

Familial gastrointestinal stromal demonstrates an autosomal dominant mode of disease inheritance wherein tumefaction exemplifies germline mutations within KIT or PDGFRα genes. Genetic mutations within SDHB subunit of succinate dehydrogenase may occur [1,2]. Sporadic or non-hereditary tumefaction can depict promoter hyper-methylation of SDHC subunit of succinate dehydrogenase. Few instances exhibit germline mutations of SDH gene [1,2].

Gastrointestinal stromal tumour deficient in succinate dehydrogenase can be accompanied by Carney triad comprised of gastrointestinal stromal neoplasms, pulmonary chondroma and paraganglioma [1,2]. Majority (~80%) of gastrointestinal stromal tumours with deficient succinate dehydrogenase may develop distant metastasis [1,2]. Carney-Stratakis syndrome is constituted of gastrointestinal stromal tumour and paraganglioma. The hereditary condition exhibits an autosomal dominant mode of disease transmission and germline mutations within SDHB, SDHC or SDHD subunit of succinate dehydrogen-

ase gene [1,2]. Gastrointestinal stromal tumour deficient in succinate dehydrogenase generally emerges within distal stomach or antrum. Tumefaction exhibits a female preponderance with a female to male proportion of 2;1. Neoplasm commonly implicates young adults < 40 years or paediatric subjects [1,2].

Subjects afflicted with neurofibromatosis 1 (NF1) may represent with singular or multiple gastrointestinal stromal tumours, especially within small intestine [1,2]. Commonly, tumefaction represents with gastrointestinal haemorrhage or abdominal pain [1,2].

Upon gross examination, a well circumscribed, intramural tumefaction appears centred upon muscularis propria. Cut surface is fleshy, tan or pink with focal haemorrhage or cystic degeneration. Mean tumour diameter is 6 centimetres wherein magnitude varies between 0.4 centimetre to 40 centimetres [1,2]. Cytological assessment enunciates bland, spindle-shaped to epithelioid cells configuring distinct fascicles (1,2). Upon microscopy, gastrointestinal stromal tumour preponderantly delineates histological subtypes as •spindle cell variant is comprised of bland, spindle-shaped cells imbued with faintly eosinophilic cytoplasm and configuring a syncytial pattern. Tumour cell nuclei are elongated with inconspicuous nucleoli. Para-nuclear vacuoles are commonly discerned in spindle cell gastrointestinal stromal tumour arising within the stomach [1,2]. Spindle cell gastrointestinal stromal tumour exhibits cogent subtypes as sclerosing, palisaded, vacuolated, diffuse, hyper-cellular or sarcomatoid with significant nuclear atypia and mitotic figures [1,2].

a. Epithelioid cell variant is constituted of sheets or nests of spherical cells imbued with clear to eosinophilic cytoplasm. Cellular and nuclear pleomorphism may occur [1,2]. Cogent subtypes as sclerosing, dis-cohesive, hyper-cellular or sarcomatous with significant cellular atypia and mitotic activity are observed [1,2].

b. Mixed cell variant demonstrates an admixture of spindle -shaped cells and epithelioid cells [1,2]. Tumefaction deficient in succinate dehydrogenase generally configures a multinodular tumour pattern and exhibits an epithelioid cell or mixed epithelioid cell / spindle cell morphology with minimal nuclear pleomorphism and occasional, atypical mitotic figures [1,2]. Dedifferentiated gastrointestinal stromal tumour delineates an anaplastic countenance and an unusual phenotype. Expression of KIT may be absent or aberrant expression of immune markers as cytokeratin may occur [3,4] (Table 1 & Table 2) (Figure 1 & Figure 2).

Table 1: TNM classification of gastric or omental stromal tumour [1,2].

Tumour	Node	Metastasis
TX: Primary tumour cannot be assessed	NX: Lymph nodes cannot be assessed	
T0: No evidence of primary tumour	N0: Regional lymph node deposits absent	M0: Distant metastasis absent
T1: Tumour magnitude ~2cm	N1: Tumour deposits in regional lymph nodes	M1: Distant tumour metastasis
T2: Tumour magnitude between 2cm to 5cm		
T3: Tumour magnitude between 5cm to 10 cm		
T4: Tumour magnitude > 10cm		

Table 2: TNM classification of intestinal or peritoneal stromal tumour [1,2].

Tumour	Node	Metastasis
TX: Primary tumour cannot be assessed	NX: Lymph nodes cannot be assessed.	
T0: No evidence of primary tumour		
T1: Tumour magnitude ~2cm	N1: Tumour deposits in regional lymph nodes	M1: Distant tumour metastasis
T2: Tumour magnitude between 2cm to 5cmA		
T3: Tumour magnitude between 5cm to 10 cm		
T4: Tumour magnitude > 10cm		

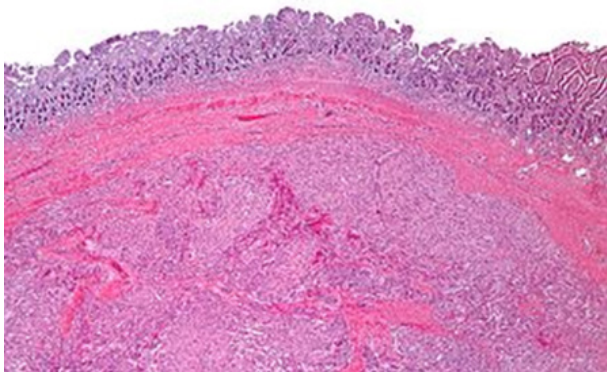

Figure 1: Gastrointestinal stromal tumour demonstrating intramural tumour cell nests segregated by vascularized fibrous tissue septa and intact superimposed mucus-secreting columnar epithelium [5].

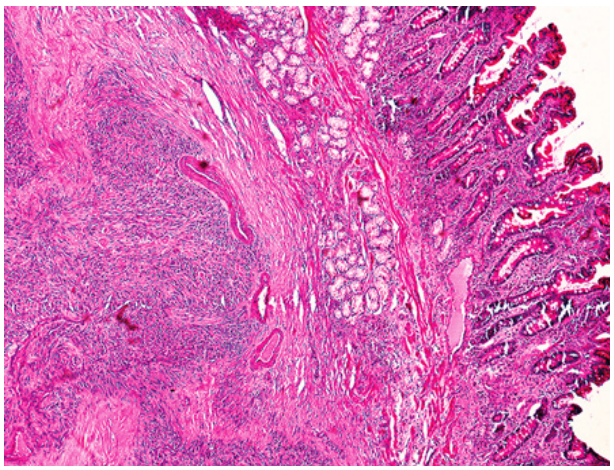

Figure 2: Gastrointestinal stromal tumour of duodenum depicting aggregates and fascicles of spindle-shaped cells centred upon muscularis propria with superimposed mucosal papillae layered with columnar epithelium [6].

Stage I and stage II neoplasms are low grade lesions with minimal mitotic activity (≤ 5 per 50 high power fields) whereas stage III and stage IV tumefaction are high grade neoplasms with enhanced mitotic activity (>5 per 50 high power fields) [5,6].

Gastrointestinal stromal tumour is immune reactive to ANO1, DOG1, CD34 and smooth muscle actin (SMA). Immune reactivity with CD117 exhibits a membranous or dot-like perinuclear pattern or diffuse cytoplasmic reactivity [5,6]. Tumour cells are immune non reactive to S100 protein and SDBH subunit of succinate dehydrogenase [5,6]. Gastrointestinal stromal tumour requires segregation from neoplasms such as leiomyoma, schwannoma or solitary fibrous tumour [5,6]. Generally, imaging features are variable and contingent to tumour magnitude and duration of tumour representation [5,6]. Endoscopic, ultrasound- guided, fine needle aspiration can be adopted for preliminary tumour discernment [5,6]. Upon endoscopy, a sub-epithelial tumefaction is observed which requires confirmation with cogent histological examination [5,6]. Endoscopic ultrasonography exemplifies a solid, hypoechoic neoplasm [5,6]. Computerized tomography (CT) enunciates a solid, heterogeneous tumefaction with focal haemorrhage or cystic degeneration [5,6]. Majority of gastrointestinal stromal tumours are optimally treated with comprehensive surgical extermination [5,6]. Tyrosine kinase inhibitor as imatinib mesylate is recommended for treating neoplasms with KIT and PDGFRα genetic mutations or reoccurring gastrointestinal stromal tumours demonstrating distant metastasis. Additionally, tyrosine kinase inhibitors of KIT, PDGFRα and VEGFR such as sunitinib malate can be employed [5,6]. Neoplasms deficient to succinic dehydrogenase (SDH) appear minimally responsive to tyrosine kinase inhibitors [5,6].

Comprehensive surgical eradication of neoplasm delineates decimated proportionate localized tumour reoccurrence and enhanced overall survival [5,6]. Inadequate surgical extermination, especially of rectal neoplasms, is associated with enhanced tumour reoccurrence. Intraoperative tumour rupture exemplifies inferior therapeutic outcomes [5,6].

References

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5. Figure 1 Courtesy: Libre pathology.
6. Figure 2 Courtesy: Research gate.s