MULTIFOCAL GASTRIC EPITHELIOID GASTRO-INTESTINAL STROMAL TUMOUR IN A 12 YEAR OLD GIRL - A CASE REPORT

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Abstract:
Most gastrointestinal stromal tumours (GISTs) are driven by KIT or PDGFRA (Platelet Derived Growth Factor Activator) activating mutations, but a small subset is associated with loss of function of the succinate dehydrogenase (SDH) complex of mitochondrial inner membrane proteins. This occurs via germline mutations of the SDH subunit genes and certain other unknown mechanisms. SDH-deficient GISTs especially include pediatric GISTs and those associated with Carney triad (CT) or Carney-Stratakis syndromes (CSS) the latter two also include paraganglioma as a component(1). These tumours show specific clinicopathological features such as female preponderance, onset in childhood, gastric location, multifocality and epithelioid morphology. We present a case of SDHB negative multifocal gastric GIST with epithelioid morphology in a 12 year old female child.

Keyword: SDHB, GIST, Imatinib, KIT, PDGFRA

Introduction:
GISTs are the most common mesenchymal neoplasms of the gastrointestinal tract. Gain-of-function somatic mutations of the KIT or PDGFRA genes represent the most prevalent molecular alterations in GISTs (2). A unique subgroup of GIST is driven by dysfunction of the mitochondrial complex 2 composed of succinate dehydrogenase A (SDHA), SDHB, SDHC and SDHD. These SDH deficient GISTs show distinct clinical and morphological features including frequent onset in childhood and young adulthood, gastric location, a tendency to multifocality, absence of KIT and PDGFRA mutations (wild type GISTs), a prognosis not predicted by size and mitotic rate and a tendency to indolent behaviour of metastases(3). They do not respond to Imatinib(4), but may respond better to Sunitinib. Negative staining for SDHB is characteristic of the GISTs of the Carney triad and the subgroup of paediatric GISTs they resemble (that is, paediatric wild type GISTs).
Case report: A 12 year old girl child was brought with history of malaena and anaemia of 10 months duration. CT abdomen showed thickening of the gastric wall along the greater and lesser curvatures measuring up to 12mm in the body and antral regions. A well-defined, intraluminal polypoidal mass lesion was seen in the antral region along the lesser curvature measuring ~3.5x3.2cm with heterogenous enhancement. Wall thickening was also seen along the antral and pylorus regions with luminal narrowing. There was no significant lymphadenopathy or any other intra-abdominal tumour. Chest X-ray ruled out any lung lesions. There was no significant family history. Intra-operatively there was a large 5cm exophytic tumour in the antrum. Two other smaller nodules 1cm in size and 5mm size were seen adjacent to the main tumour. No perigastric nodes were identified. Subtotal gastrectomy was performed.

Pathologic findings: Gross examination: Distal gastrectomy specimen showed a nodule on the serosal surface, 0.8x0.8x0.6cm with a grey-brown haemorrhagic cut surface with focal white areas. Anterior surface showed nodularity at the distal resection end (Fig.1). On opening, there was a submucosal nodular swelling along the lesser curve, 3x2.6x2.4cm with surface ulceration and a grey-white firm cut surface (Fig.2). One lymph node, 0.8cm in diameter was present in the greater omental fat.

Microscopy: Sections from the large submucosal nodule (Fig.3) showed a partially circumscribed tumour arranged in loose sheets, trabeculae and nests of polygonal cells with mildly pleomorphic, round to oval, vesicular nuclei with dispersed chromatin, inconspicuous nucleoli and moderate amounts of pale eosinophilic cytoplasm. Mitotic activity was up to 3/50 hpf. Stromal sclerosis was present. There was no haemorrhage or necrosis. The tumour was seen infiltrating muscularis propria but definite breach of serosa was not seen. On immunohistochemistry (IHC), the tumour cells were positive for CD117 and CD34 and negative for SMA and S100. Sections from the smaller serosal nodule (Fig.4) showed a partly encapsulated tumour composed of cords and interlacing trabeculae of medium-sized round cells with round to oval nuclei, fine chromatin, inconspicuous nucleoli and eosinophilic cytoplasm. The mitotic activity was >5/10 hpf. IHC for CD117 and DOG1 were positive (Figs. 5 and 6). CD34, CD56, synaptophysin and chromogranin were negative. IHC for SDHB showed absent staining in the tumour cells and normal cytoplasmic granular staining in the stromal vascular endothelial cells and lymphocytes (Fig.7). The greater omental lymph node was free of tumour. Based on morphology and immunohistochemistry, a diagnosis of SDHB negative multifocal gastric epithelioid GIST was made.
Fig.1. Subtotal gastrectomy specimen showing a nodule on the serosal aspect.

Fig.2. Mucosal surface of stomach showing a submucosal nodular swelling with grey-white to tan cut surface.

Fig.3. Large submucosal nodule showing tumour arranged in sheets and trabeculae of epithelioid cells. (H&E stain; original magnification x 200)

Fig.4. Serosal nodule showing tumour arranged in interlacing trabeculae of epithelioid cells. Mitotic figures are seen. (H&E stain; original magnification x 400)

Fig.5. CD117 immunostain showing diffuse and strong cytoplasmic positivity in the tumour cells. (Original magnification x 200)

Fig.6. DOG1 immunostain showing cytoplasmic membrane positivity in the tumour cells. (Original magnification x 400)
Discussion: Paediatric GISTs show a marked female predominance and nearly always arise in the stomach, where they are often multifocal(5). GISTs of the paediatric wild-type, GISTs from the mult tumour Carney–Stratakis syndrome, and GISTs associated with the Carney triad (GIST, pulmonary chondroma and paraganglioma) share certain clinicopathological properties that include early-onset, multifocal GISTs with epithelioid cell morphology and absence of KIT/ PDGRFA mutations(6), suggesting a common aetiology. Carney–Stratakis is an inherited disorder associated with GIST and paragangliomas caused by germline mutations in SDH genes. The connection between defective cellular respiration and GIST pathology has been strengthened by the utilization of SDHB immunohistochemistry to identify SDH deficiency in paediatric GISTs, syndromic GISTs and some adult wild-type GISTs(7).

Although our patient was young and had multifocal GIST, there was no family history of GIST or evidence of pulmonary chondroma or paraganglioma on radiology. It is recommended that GISTs of epithelioid cell morphology be tested for SDHB immunohistochemically. In case of negative SDHB staining in GISTs, Carney-Stratakis syndrome or Carney triad should be considered and appropriate clinical surveillance should be instituted (8). Risk stratification based on the most commonly used system for assessing the malignant potential of GISTs (Armed Forces Institute of Pathology) does not seem to predict the clinical behaviour of these tumours(5). SDHB negative GISTs show very characteristic morphological and clinical features which if recognized, can lead to IHC for SDHB and therefore definite diagnosis. Early diagnosis of SDH-related neoplasia is advantageous in view of the distinct natural history of these tumours and the potential for genetic testing and screening to alleviate disease burden in these families. In conclusion, a central role of SDH dysregulation has recently been established in wild type GIST oncogenesis(9). SDH-deficient GISTs demonstrate unique clinical and pathological features, including an exclusively gastric location, absence of KIT or PDGFRA mutations, primary resistance to Imatinib and a tendency to develop multifocality and metachronous tumorigenesis.(4).

Bibliography:


