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A CASE SERIES OF ULNAR NERVE PARESIS IN GASTROINTESTINAL STROMAL TUMOUR PATIENTS

General Surgery

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ABSTRACT

Background: With the rise in the incidence of gastrointestinal stromal tumors (from 0.55 per 100,000 population in 2001 to 0.78/100,000 in 2011.), a clear understanding of this condition and its various manifestations has become quite essential. Although a rare manifestation, the occurrence of ulnar nerve paresis in patients diagnosed with gastrointestinal stromal tumours is frequent enough to warrant research into its causation. This series report three cases of isolated ulnar nerve paresis in four patients diagnosed with gastrointestinal stromal tumours, with the aim of assessing the occurrence of nerve pathology in these tumours and a brief review of the literature on its clinical presentation and therapeutic approach. **Methods:** A case series of three cases of ulnar nerve paerisis reported in patients operated for gastrointestinal stromal tumour were analysed by terms of tumour morphology, histopathological examination and immunohistochemistry. **Results:** There was a strong association found to be noted in GIST cases with immunohistochemistry showing S-100 positivity **Conclusion:** The occurrence of extra intestinal manifestations, although not documented extensively, isn't something entirely unheard of. In 3 documented cases of GIST at Government Medical College and ESI Hospital, Coimbatore, the development of right ulnar nerve paresis postoperatively is to be noted among S-100 marker positive cases. Patients complained of weakness of right hand postoperatively, and were treated promptly with adjuvant chemotherapy and recovered.

KEYWORDS

GIST, Immunohistochemistry, Imanitib, ulnar nerve.

INTRODUCTION:

Gastrointestinal stromal tumours[1] are the most common mesenchymal tumours of gastrointestinal tract. Even though well documented, statistical data regarding the incidence of GIST in India isn't available and its treatment modality is largely procured from studies in other foreign populations.

They occur commonly in stomach (60%), small intestine (30%), rectum (3%), colon (2%), oesophagus (<1%) and rarely in omentum and mesentry. They originate[2] from the muscle wall of the GI tract and attached to the outer aspect of gut. GIST are proposed to arise from the interstitial cells of Cajal. About 85% of GIST contain oncogenic mutations in one of two receptor tyrosine kinases: KIT or PDGFRA (platelet-derived growth factor receptor alpha). Size varies from 1cm to 40cm. Morphologically they may be composed of spindle cells (70%), Epithelioid cells (20%) and mixed spindle and epithelioid cells (10%). Patients clinically present commonly with history of GI bleeding followed by acute abdomen due to tumour rupture, gastrointestinal obstruction and pain. Smaller lesions are incidentally found during surgery, radiological [3] studies and scopy. Advanced disease metastases to liver, lung and bone. Brain metastases are rare. Diagnostic interventions include contrast enhanced computed tomography, magnetic resonance imaging, upper GI endoscopy and endoscopic ultrasound with FNAC and 18FDG-PET. Most commonly used marker[4] for GIST is the CD117 antigen an epitope of the KIT receptor tyrosine kinase. It will be positive in approximately 95% of GIST. Treatment modalities include surgical resection and molecular-targeted therapy with KIT/PDGFRA tyrosine kinase inhibitors such as imatinib mesylate or sunitinib malate. Median disease-specific survival of patients with metastatic GIST was 19 months. Prognosis in GIST was influenced by mitotic index (mitoses per 50 hpf), tumour size and tumour location.

Rarely GIST present with extra intestinal manifestation[5]. Although uncommon, thorough research into the causation of these extra intestinal presentations might prove to be of immense wealth in finding out better treatment modalities.

One such manifestation appears to be ulnar nerve paresis, and hence, this case series report three cases of isolated ulnar nerve paresis in patients diagnosed with gastrointestinal stromal tumours, with the aim of assessing the occurrence of nerve pathology in these tumours and a brief review of its literature.

CASE 1: (SEP-2017)

A 38-year-old male presented to the Emergency ward as a case of perforative peritonitis; He had h/o abdominal pain for 2 days and constipation for 3 days; Chest x-ray showed air under diaphragm and ultrasound abdomen showed sluggish peristalsis in few bowel loops.

Hence proceeded with laparotomy; There was a 1x0.5cm perforation in terminal ileum 30cm proximal to ileocolic junctions; Also, there was a 6x4cm tumor distal to the perforation in ileal wall (Fig. 1). Excision of tumor with ileal segment resection and anastomosis done.

Post operatively patient had ulnar paresis on right side around 10th post-operative day; Nerve conduction studies showed decreased potentials in right ulnar nerve below elbow.

Specimen Immunohistochemistry showed CD117, CD34, DOG-2, S-100 positivity.

Postoperatively adjuvant chemotherapy-Imatinib[8] was started around 45 days; In about 2 months, patient recovered from right ulnar nerve paresis

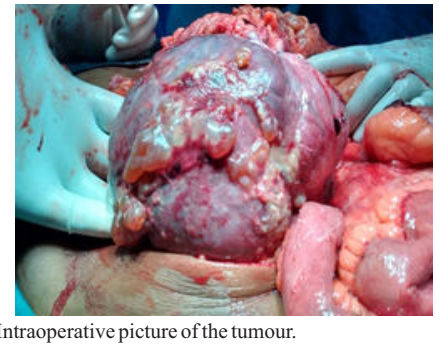

Fig. 1 – Intraoperative picture of the tumour.

CASE 2: (NOV 2017)

A 57-year-old male presented to Emergency ward as a case of acute intestinal obstruction; He had h/o constipation for 6 days and acute abdominal pain associated with vomiting; USG-abdomen and CT-abdomen showed 5x5cm lump adherent to small intestine; probably GIST.

Hence, proceeded with laparotomy; there was a tumor (5x5cm) adherent to jejunal wall; Resection of jejunal segment with tumor and normal segments anastomosed.

Post operatively patient had ulnar paresis on right side around 10th post-operative day; Nerve conduction studies showed decreased potentials in right ulnar nerve below elbow.

Specimen Immunohistochemistry showed CD117, CD34, DOG-2, S-100 positivity.

Postoperatively adjuvant chemotherapy-Imatinib was started around 45 days; in about 2 months, patient recovered from right ulnar nerve paresis

CASE 3: (APRIL 2018)

36 year old male admitted with history of abdominal pain for 1 day and absolute constipation for 1 day. No history of vomiting. He was hemodynamically unstable and abdominal examination showed diffuse guarding and suspected mass over right hypochondrium, right lumbar, epigastric and umbilical region. Paracentesis was of haemorrhagic tap.

Biochemical investigations were within limits. X-ray chest and abdomen erect showed air under right hemi diaphragm (Fig. 2). Hence proceeded with contrast enhanced computed tomogram which revealed a 15*12*10 cm solid mass over right side of abdomen (Fig. 3), but its organ of origin was not able to identify. Hence proceeded with emergency laparotomy. Intraoperatively there was about 1.4 litre of hemoperitoneum. There was a huge tumour of about 15*15 cm in size with active bleeding from its surface and necrosed area noted. Its pedicle was traced and it was attached to the duodenum. Kocherization done and it was attached to the duodenum and near total excision of tumour done. Primary repair of a rent of about 2*1cm in the duodenum done. Peroperatively 8 units of B-positive blood transfused. Postoperatively elective ventilation continued for 2 days. Oral feeding started on 4th day and patient tolerated well. Histopathological report came out to be of gastrointestinal stromal tumour. The tumour showed moderate cellularity and mixed epithelioid and spindle cells arranged in fascicles (Fig. 4) with a low mitotic count (1/50 high power field) and areas of necrosis. It was subjected to immunohistochemistry markers and revealed positivity for CD-117 (Fig. 5) and diffuse, strong positivity of DOG-1 markers (Fig. 6) confirming GIST.

Patient is on periodic follow-up and started on adjuvant imatinib therapy.

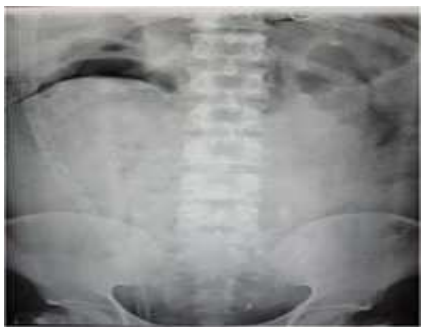

Fig. 2 – air under diaphragm in x-ray abdomen erect.

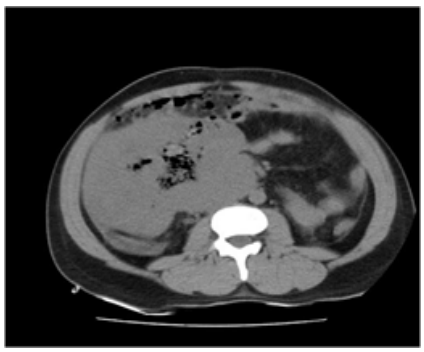

Fig. 3 – CECT showing a intraperitoneal solid mass occupying right side of abdomen and free fluid.

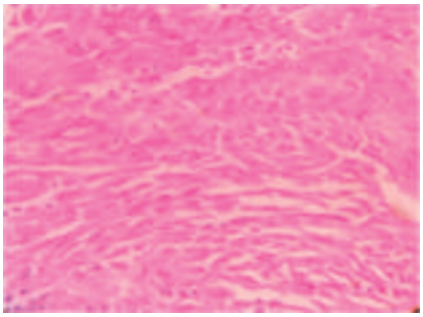

Fig. 4 – HPE showing mixed spindle and epithelioid cells.

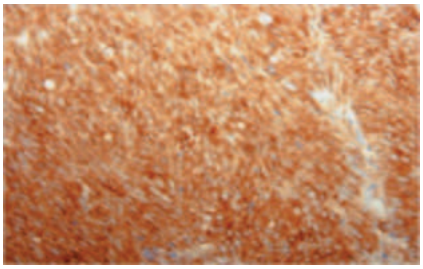

Fig. 5 – CD-117 positivity.

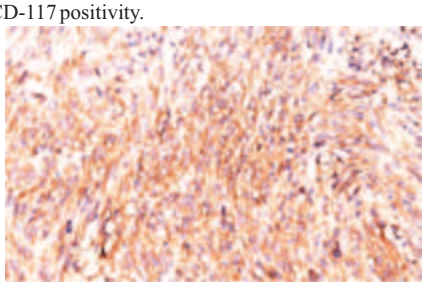

Fig. 6 – DOG-1 positivity.

CASE 4: (MAY-2018)

A 42-year-old male presented to emergency casualty as a case of acute abdominal pain for 1 day; Radiological investigations showed a tumor at stomach with irregular surface and hemoperitoneum.

Laparotomy done and there was a huge GIST arising from antropyloric region of stomach with tumor perforation; Resection tumor done.

Post operatively patient had ulnar paresis on right side around 10th post-operative day; Nerve conduction studies showed decreased potentials in right ulnar nerve below elbow.

Specimen Immunohistochemistry showed CD117, CD34, DOG-2, S-100 positivity.

Postoperatively adjuvant chemotherapy-Imatinib was started around 45 days; In about 2 months, patient recovered from right ulnar nerve paresis.

DISCUSSION:

Gastrointestinal Stromal Tumors, although making up less than 1% of all gastrointestinal tumors, are the most commonly occurring mesenchymal tumors of the GI tract. Even though they are the most commonly occurring visceral soft tissue sarcomas, the incidence of this condition is unclear as they often remain unnoticed.

Gastrointestinal stromal tumors are believed to arise from the interstitial cells of Cajal, within the gastrointestinal myenteric plexus. They commonly arise from the stomach, small intestine and rectum. Interstitial cells of Cajal and GIST share common markers for CD117 and DOG1. The most common mutation causing GIST occurs in the *KIT* gene (70%), which codes for a tyrosine kinase receptor, c-kit. Mutations[6] in other genes like PDGRα, SDH, BRAF, NF1 and KRAS also have the potential to cause GIST. GISTs can occur both sporadically and also part of syndromes like Neurofibromatosis-1, Carney-Stratakis syndrome and Von-Hippel-Lindau syndrome. Although previously described as leiomyoma or leiomyosarcoma, they are differentiated on the basis of CD34, CD117 and DOG1 along

with the lack of smooth muscle staining.

The clinical manifestations [7] range from non-specific symptoms like nausea and vomiting to more specific manifestations like pain or gastrointestinal bleeding. They're either recognized by the ulcerating mucosa overlying them, which leads to bleeding, or by incidental endoscopy.

The occurrence of extra intestinal manifestations, although not documented extensively, isn't something entirely unheard of. In four documented cases of GIST at Government Medical College and ESI Hospital, Coimbatore, three cases had development of right ulnar nerve paresis postoperatively to be noted. Patients complained of weakness of right hand postoperatively, and were treated promptly.

On endoscopic examination, GISTs appear as a smooth submucosal tumor that impinges on visceral lumen. The differential diagnoses range from neuroendocrine tumor, intramural lipoma, lymphoma, etc. CT imaging shows that these tumors are well-encapsulated and show heterogenous contrast enhancement due to regions of necrosis within the tumor. An endoscopic ultrasound-guided needle biopsy generally shows a spindle cell neoplasm.

When subjected to immunohistochemical studies, GIST return positive for CD37, CD117 and DOG1. These three markers, thus form the cornerstone of diagnosis. The specimens in discussion on the other hand, tested positive for CD117, DOG1 and S100 tumor markers.

Current treatment modalities[9] are restricted to surgical resection and adjuvant chemotherapy. The 2–5-year recurrence-free survival rates are usually estimated based off of the nomogram developed by The Memorial Sloan-Kettering Cancer Center based on the size of the resected tumor, mitotic rate and anatomic site of origin. These prognostic tools are also used to measure the efficacy of the adjuvant chemotherapy prescribed. A course of adjuvant Imatinib has proved to revolutionary in controlling recurrence rates and post-operative complications. The patients under study too, were subjected to adjuvant Imatinib therapy for 45 days post-operatively, following which their symptoms subsided.

This case series, albeit being a fairly small sample size, has brought to our attention the occurrence of extra-intestinal manifestations of gastrointestinal stromal tumors. The presence of S100 is usually a marker found in association with nerve cell tumors. This finding, coupled with the neurological manifestation experienced, opens up the avenue for discussion regarding GIST being a possible paraneoplastic syndrome. Neoadjuvant Imatinib therapy may also be tested to see if it's a better alternative. This study, when performed on a larger scale, will open up broader treatment modalities which will help us treat GISTs more effectively.

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