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Original Research Paper

General Surgery

A CASE SERIES OF GASTROINTESTINAL STROMAL TUMOUR AND ITS VARIOUS PRESENTATION WITH MANAGEMENT

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ABSTRACT Gastrointestinal stromal tumor (GISTs) are rare mesenchymal neoplasms of the alimentary tract accounts for 0.1 -3% . GISTs arise from interstitial cells of cajal and most commonly occurs in stomach. They are best identified by computed tomography (CT) scan and most stain positive for CD117 (C-Kit), CD34, and/or DOG-1. **Aim And Objective:** The aim of the case series to analyze epidemiological aspects, clinical presentation , challenges in diagnosis , management of the diseases. **Materials And Methods;** A case series of 3 patients with GIST admitted in the DEPARTMENT OF GENERAL SURGERY IN GOVERNMENT KILPAUK MEDICAL COLLEGE AND GOVERNMENT ROYAPETTAH HOSPITAL ,CHENNAI .All 3 cases have been analyzed in this study period and followed up until discharged from the hospital **Results:** Out of three patient one patient landed up in emergency ward with obstructive features and intervened by emergency procedure, second patient presented with unusual presentation and treated by surgery with chemotherapy , and other patient presented with symptoms and treated by surgery and followed by chemotherapy. **Conclusion:** GISTs are relatively rare tumor of gastrointestinal tract. Hence a higher degree of suspicion is essential for identifying GISTs clinically. Earlier identification will help in better management. This case series shows 3 possible clinical presentations of GIST.

KEYWORDS :

2. INTRODUCTION

Gastrointestinal stromal tumour (GISTs) are the most common mesenchymal tumour of the gastrointestinal tract and are believed to originate from the interstitial cells of Cajal. GISTs have a slight male predominance and arise most commonly from the stomach or small intestine, with a median age of 60 years at presentation. Although surgery remains the treatment of choice for localized tumour, imatinib mesylate and more recently sunitinib malate, both specific inhibitors of the KIT tyrosine kinase function, have revolutionized the management of unresectable, recurrent, and metastatic GISTs. The treatment paradigm for GISTs has undergone a dramatic advancement and is increasingly being studied as a model for a multidisciplinary approach involving surgery and targeted molecular therapy for management of other solid tumour.

3. AIM AND OBJECTIVES

The aim of the case series to analyze epidemiological aspects, clinical presentation , challenges in diagnosis , management of the diseases.

4. Review of Literature

What is now known as GIST, used to be called gastrointestinal (GI) smooth muscle tumour: leiomyoma if benign, leiomyosarcoma if malignant, and leiomyoblastoma if with epithelioid histology. Tumour previously classified as gastrointestinal autonomic nerve tumour have also turned out to be GISTs, as have many tumour historically classified as gastrointestinal schwannomas or other nerve sheath tumour. Electron microscopic studies from the late 1960's and on demonstrated that most of the "GI smooth muscle tumour" differed from typical smooth muscle tumour by their lack of smooth muscle-specific ultrastructure. Immuno histochemically they lacked smooth muscle antigens, especially desmin. As they also lacked Schwann cell features, gastrointestinal stromal tumour was then proposed as a histogenetically non-committal term for these tumour. The discovery of KIT expression and gain-of-function KIT mutations in GIST in 1998 was the basis of the modern concept of GIST – a generally KIT positive and KIT mutation-driven mesenchymal neoplasm specific to the gastrointestinal tract. GIST, once considered and obscure tumour, is now known to occur with an incidence of at least 14–20 per million, by population-based studies from northern Europe. These estimates represent the minimum incidence, as subclinical GISTs are much more common. In an US study, 10% of well-studied resection specimens of gastroesophageal cancer harbored a small incidental GIST in the proximal stomach. An autopsy study from Germany also found a 25% incidence of small gastric GISTs. Despite occasional reports to the contrary, we do not believe that GISTs primarily occur in parenchymal organs outside the GI tract at sites such as the pancreas, liver, and gallbladder. At the two first mentioned organs, GISTs are metastatic or direct extensions from gastric or duodenal, or other intestinal primary tumour. We are skeptical about primary GISTs in the gallbladder and note that the reported evidence for this diagnosis is tenuous and that molecular genetic documentation is absent. Furthermore, review of all gallbladder sarcomas in the AFIP failed to find any GISTs. Similarly, GISTs diagnosed in prostate biopsies are of rectal or other gastrointestinal and not prostatic origin .

5. MATERIAL AND METHODS

A case series of 3 patients with GIST admitted in the Department Of General Surgery In Government Kilpauk Medical College And Government Royapettah Hospital, chennai. All 3 cases have been analysed in this study period and followed up until discharged from the hospital

6. RESULTS (INCLUDING OBSERVATIONS)

Case Report 1:

45 year old male came with chief complaints of abdominal distension, abdominal pain, constipation and vomiting for 4 days and no comorbidities.

Past history:

He had history of abdominal pain 5 years back and radiological investigation revealed diffusion restricting mass lesion in left iliac fossa adjacent to small bowel loop -?GIST . Computered tomography guided biopsy and immuno histochemistry of the blocks showed positivity of CD117 and

patient proceeded with laparotomy and en bloc resection of tumour with end to end jejunojejunal anastomosis done, post operatively patient treated with imatinib mesylate. After completion of imatinib mesylate computered tomography screening done and it revealed no residual lesion .

Current Scenario:
Patient advised for x ray abdomen erect reveals - multiple dilated bowel loops with air fluid levels (figure1). Contrast enhanced computered tomography abdomen and pelvis revealed -multifocal heterodense lesion adjacent to 2 and 3 rd part of duodenum , desecending colon and sigmoid colon appears collapsed, heterodense lesion noted anterior to stomach and multiple air fluid levels with maximum dilatation of 6.5cm (figure 2).

Intraoprative Findings :
Multiple gist noted in jejunum, ileum and mesentry.(figure 3). A Mass of size approximately 10*6 cm noted about 60cm from ileocaecal valve with collapsed ileum distally.(figure 4). A mass of size 13*7 cm noted in hepatic flexure and proximal transverse colon (figure 5).

Decision Made:
Resection Of Tumour At Hepatic Flexure Proximal Transverse Colon And Mesocolon. Resection Of Tumour At Ileum. Milking Of Proximal Small Bowel. Side To Side Anastomosis Of Ileum And Transverse Colon. Multiple Small Gists At Ileum Jejunum Mesentry

Excised (figure 6). Histopathology :
Interlascing fascicles storiform pattern of spindle shaped cells having hyperchromatic elongated nuclei exhibiting moderate pleomorphism with >5/5 mm square mitotic figures.

Pathological Stage :
pT4(m) according to 8 th edition AJCC. CHEMOTHERAPY : In view of recurrence of GIST along with high grade mitotic index combined with multiple in number the patient was started on imatinib mesylate high dose . Patient advised for CT SCREENING for every 6 months.

Case Report 2:
A 64 male with chief complaints of abdominal distension and vomiting for 1 week with history of melena for 1 week frequency increased in last 2 days (10 episodes).on examination Patient found to be dehydrated , hypotension and tachycardia and pallor present. On per abdomen examination :Fullness seen in right hypochondrium extending to right lumbar region .A mass of size 15*8cm was palpable in right hypochondrium and extending to right lumbar region, smooth surface, hard in consistency, finger insinuation present between the mass and coastal margins. Dullness on percussion over the mass. Patient resuscitated with intravenous fluids and blood and blood products

Investigations:
Severe anemia was present. Elevated renal parameters. Other parameters were within normal range. CT abdomen and pelvis: Heterogenous Soft tissue mass lesion measuring 15*8.5*10 cm noted arising from the pylorus with internal air pockets and surrounding inflammation (figure 7). Intraoperative findings: A mass of size 12*8*10 cm, arising from distal part of stomach was found. Resection of the mass in toto along with distal gastrectomy and gastro-jejunal anastomosis was done. resected specimen sent for hpe (figure8).

Histopathology :
Tumor shows well circumscribed malignant neoplasm just beneath the mucosa of the stomach consisting of spindle shaped cells with moderate cytoplasm. Mitotic figures >5/50 high power fields (HPF). Margins uninvolved. pTMN staging-pT4Nx Immunohistochemistry–CD117-intense cytoplasmic positivity in 80% of tumour cells. patient advised for chemotherapy imatinib mesylate and followed up .CASE REPORT 3: 45 year old female came with complaints of mass over the abdomen ,history of ball rolling movements present, and history of loss of weight and loss of appetite for 2 months .patient had no comorbidities. On per abdomen examination ill defined mass visible in epigastrium and left hypochondrium , tenderness in left hypochondrium ,no guarding , no rigidity . Routine blood investigation revealed normal . serum lipase within normal range. USG ABDOMEN AND PELVIS :11.6*6 cm heteroechoic ill defined lesion noted at the tail of pancreatic region with minimally internal vascularity. CT abdomen and pelvis revealed :10*8cm minimally enhanching soft tissue dense exophytic growth noted at posterior aspect and body of stomach indending spleen and tail of pancreas -features suggestive of GIST (figure 9).

Impression :gist Stomach. S/p: Sleeve Gastrectomy(figure 10) Hpe report specimen + for CD117& CD 34. Patient advised for chemotherapy-imatinib mesylate and followed up.

7. DISCUSSION

GISTs represent more than 80% of all mesenchymal tumour found in the gastrointestinal tract, though they account for only approximately 3% of all gastrointestinal malignancies. Historically, various terms and acronyms have been used to describe GISTs such asleiomyomas, leiomyoblastomas, leiomyosarcomas, gastrointestinal autonomic nerve tumour (GANT), smooth muscle tumour of uncertain malignant potential (STUMP), and, most recently, gastrointestinal pacemaker cell tumour (GIPACT). These variable classifications could be attributed to a wide array of conflicting histopathologic and electron microscopic features recognized over the past 20 years. It was only in the late 1990s that their distinct cell of origin was identified, and it was shown that GISTs share morphologic, immunophenotypical, and genetic characteristics with the interstitial cells of Cajal. It has now been well established that GISTs arise from the interstitial cells of Cajal, which are specialized pacemaker cells located around the myenteric plexus of the gut wall, particularly in the stomach and small intestine. More than 90% of GISTs result from gain-of-function mutations of the c-KIT/KIT proto-oncogene. KIT encodes for the transmembrane KIT receptor tyrosine kinase. Under physiologic conditions, when the KIT tyrosine kinase receptor is stimulated by its ligand or stem cell factor (also known as steel factor or mast cell growth factor), it is associated with cellular proliferation, differentiation, maturation, survival, chemotaxis, and adhesion. GISTs result from constitutive tyrosine kinase activation (ligand-free activation) by a gain-of-function mutation, which leads to unregulated cell growth and proliferation, resistance to apoptosis, and eventual malignant transformation. Most KIT mutations occur as deletions and insertions or point mutations in the juxtamembrane domain encoded by exon 11 (70%). Less commonly, they occur in the extracellular region encoded by exons 9 (14%), 13 (4%), or 17 (2%), all of which encode the tyrosine kinase domain.

Approximately 10% of GISTs result from mutations in the KIT-related kinase gene, platelet derived growth factor receptor alpha (PDGFRA). They are seen more often in exon 18 (5.6%) and very rarely in exons 12 (1.5%) and 14 (0.5%).

A small percentage of GISTs are wild-type, and some may also be part of familial syndromes such as von Recklinghausen neurofibromatosis (NF1) and the Carney triad (GIST, paraganglioma, and pulmonary chordoma). A Swedish study reports a 500-fold increased incidence of GISTs in patients with NF1. GISTs vary in size from less than 2 cm to as large as 20 cm, and they can be submucosal,

intramural, or subserosal. Smaller tumour (<2 cm) are usually asymptomatic, and they are generally detected incidentally on endoscopy, radiologic imaging, or laparotomy performed for other indications. GISTs tend to displace adjacent tissue and organs without truly infiltrating them and hence can grow remarkably large prior to becoming symptomatic. Symptoms depend largely upon the anatomic location and size of the tumour. In two studies published recently, symptomatic tumour were approximately 7 cm in size, asymptomatic tumour were 2 cm, and GISTs detected at autopsy were approximately 1.5 cm. Approximately 70% of GISTs are symptomatic at presentation, 20% are asymptomatic and found incidentally, and approximately 10% are found at autopsy. Nonspecific symptoms such as nausea, vomiting, bloating, abdominal pain or discomfort, or increased abdominal girth are commonly seen. GISTs located submucosally often cause ulceration of the overlying mucosa, which leads to melena. Hematemesis or hematochezia is rarely a presenting symptom. As with our patient, GISTs can cause chronic occult gastrointestinal bleeding, and patients can present with melena and signs and symptoms consistent with iron deficiency anemia.

Depending upon the anatomic location, GISTs can cause dysphagia, biliary obstruction, intussusception, and, rarely, intestinal obstruction in the small bowel. Most GISTs are known to possess malignant potential and frequently metastasize to the liver (65%), followed by the peritoneum (25%), and less commonly the omentum. Lymphatic metastasis is rare, as is hematogenous metastasis to organs outside of the gastrointestinal tract, which usually occurs late in the course with fairly advanced disease. Although the literature suggests that most GISTs are symptomatic, there is a possibility that tumour are incidentally found on investigations performed for other indications. Case studies in the literature describing symptomatic GISTs generally represent patients with larger tumour that were symptomatic. More population-based studies are required to further elaborate these observational discrepancies. These tumour are usually well circumscribed and generally unencapsulated, though a pseudocapsule may be present on rare occasions. On cut sections, they vary in color from gray or white to red or brown, depending upon the degree of necrosis and hemorrhaging. Histologically, two distinct patterns have been described: spindle cell (60–70%) and epithelioid (20–30%), withapproximately 10% of GISTs demonstrating both cellular types in variable proportions.

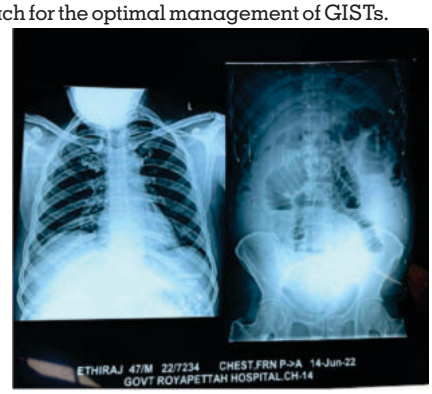
Surgery remains the modality of choice for primary, localized, and resectable GIST. Specific tyrosine kinase inhibitors (TKIs), namely imatinib mesylate and more recently sunitinib malate, have proven to be dramatically effective for unresectable, metastatic, and recurrent disease and are approved by the US Food Drug Administration for the abovementioned indications. Traditional cancer treatment modalities such as chemotherapy and radiotherapy have been shown to be ineffective while treating GIST.(figure 11) With the advent of imatinib mesylate, a specific TKI, management of GIST has been revolutionized. Imatinib inhibits cellular proliferation and promotes apoptosis in GIST cells by interrupting tyrosine kinase–mediated intracellular signaling.

Apart from c-KIT, imatinib also shows activity against several other tyrosine kinases, including PDGFRA and ABL, the Abelson proto- oncogene. The standard starting dose of imatinib for GIST treatment is 400 mg daily. There have been no significant differences in tumor response rates or duration of response using 400 mg or 800 mg of daily imatinib, and optimum dosing remains under extensive investigation. In addition, the duration of therapy has not been well defined; however, it is now known that interrupted therapy leads to disease progression in more than 60% of cases.

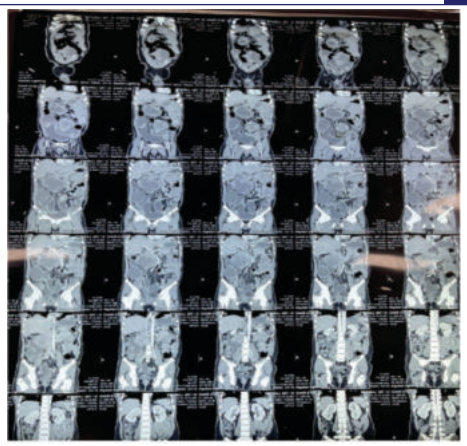
8. SUMMARY AND CONCLUSION

CONCLUSION:

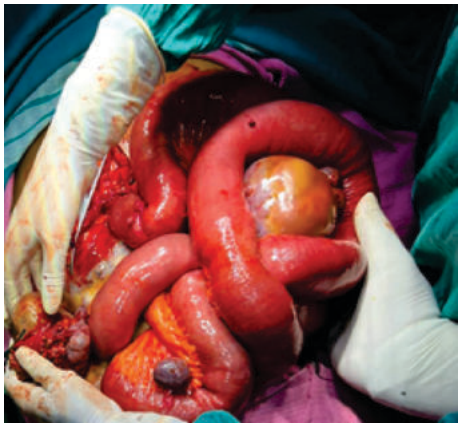
GISTs are the mesenchymal tumors of the gastrointestinal tract, and the introduction of TKIs has revolutionized the management paradigm. Out of 3 patients 2 male and 1 female, goes with usual male preponderence. In unusual acute presentation with vague symptoms GIST should be considered a differential diagnosis. Irrespective of gender STOMACH is the most common site in this study. In present era though surgery and imatinib mesylate have a upfront advantage of minimizing the occurrence of recurrent GIST infrequently recurrent GIST can occur even after complete surgical excision and conclusion of imatinib therapy(case 1) even after regular and proper follow up. Although most GISTs are asymptomatic, a significant percentage is found incidentally, and hence a high degree of suspicion should be kept in mind when examining patients. For suspected mesenchymal tumors of the gastrointestinal tract, an immunohistochemical assay for KIT (CD117) should be performed. For resectable lesion surgery still considered primary modality of management followed by chemotherapy (IMATINIB -400 mg daily =first line).Surveillance of a patient on imatinib first line therapy 6 monthly USG or 1 yearly computed tomography. Any suspicious soft tissue lesion identified during surveillance is subjected to Endoscopy ultrasonogram(EUS) /endoscopy/image guided helps in obtaining biopsy from the lesion followed by immuno histochemistry study which will arrive at diagnosis of GIST. Even in recurrent GIST if resection is possible patient can be proceeded with upfront surgery. RISK CLASSIFICATION is based on tumor size ,mitotic index, tumor site ,presence of tumor rupture (JOENSUU classification). INTERMEDIATE and HIGH RISK in JOENSUU CLASSIFICATIONS warrents adjuvant therapy. After resection recurrent GIST patient started on high dose IMATINIB (800 mg daily) subjected to regular short interval follow up(monthly /3 monthly). If non resectable or distant metstasis or if partial response or no response to high dose imatinib therapy then Patient subjected to second line tyrosine kinase inhibitor (SUNITINIB, REGORAFENIB, RIPRETINIB). Promising results have been show in clinical trials. Paucity of high level evidence investigating the management the recurrent GIST calls for prospective randomized control studies to evaluate and to design appropriate treatment protocols Molecular profiling might help in deciding the number and dosage of tyrosine kinase inhibitors in GIST recurrence. Primary and unusual locations of GIST can have unusual presentations with high chances of recurrence. GIST can never be considered as benign , long term follow up necessary .Loss of follow up or defaulter of imatinib first line therapy patient invaribly will land in recurrence or metastatic gist which have bizzare presentation. Although currently not recommended, mutational analyses for risk-profile stratification will quite likely become standards of care in the near future. Data from ongoing trials evaluating adjuvant and neoadjuvant imatinib areexpected to add more value to the current multidisciplinary approach for the optimal management of GISTs.



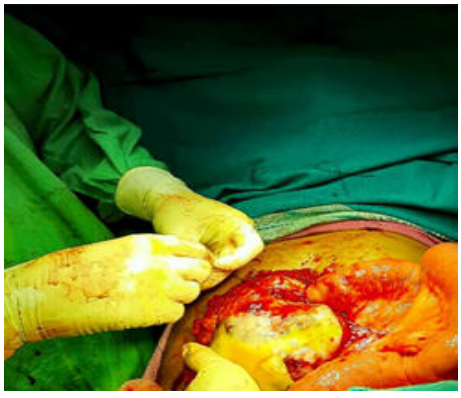
13.1 Figures Figure 1 Xray Abdomen Erect



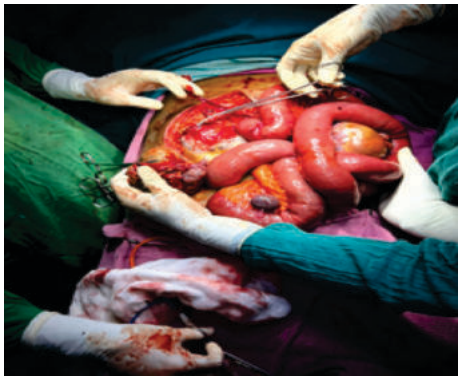
13.2 Figures Figure 2 Cect Abdomen And Pelvis



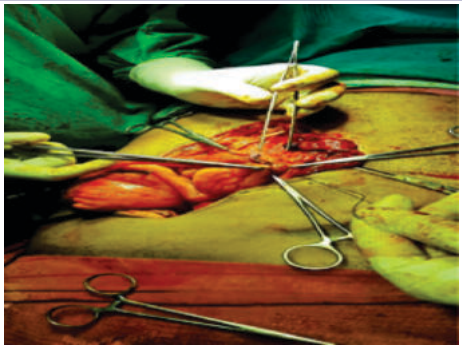
13.3 Figures Figure 3 :multiple Gist Noted In Jejunum Ileum Mesentry



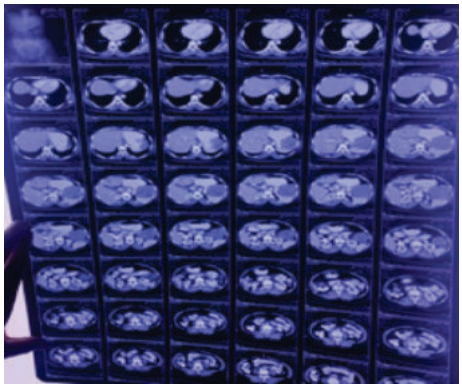
13.4 Figures Figure 4 : Mass Noted From 60cm Ileocaecal Valve



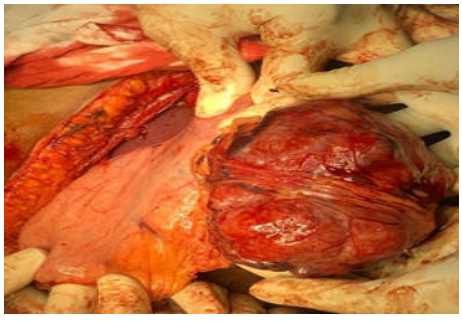
Figures Figure 5: A Mass Of Size 13*7 Cm Noted In Hepatic Flexure And Proximal Transverse Colon With Collapsed Rest Of Colon



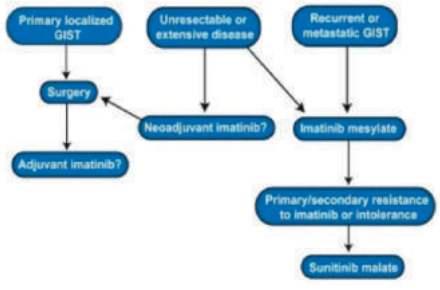
13.6. Figures Figure 6: Side To Side Anastomosis Of Ileum And Transverse Colon



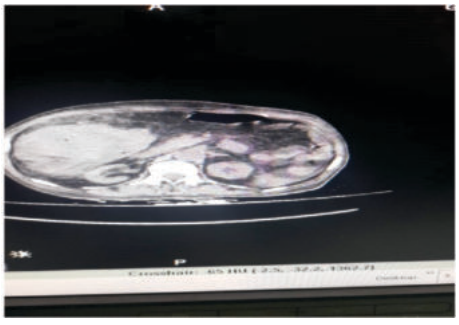
13.9 Figures Figure 9: Ct Abdomen Pelvis



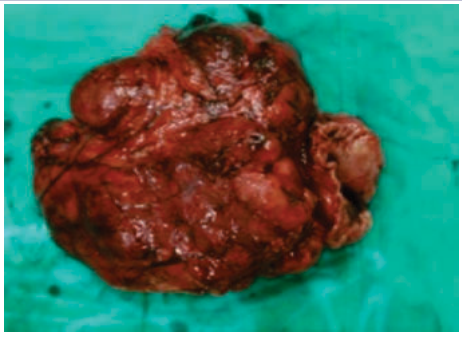
13.10 Figures Figure 10 Gist In Stomach



13.11 Figures Figure 11 :management Of Gist



13.12 Figures Figure 7 Ct Abdomen And Pelvis



13.13 Figures Figure 8 Post Resection Specimen Of Gastric Gist

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