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Case report

# Refractory hypoglycaemia in a localised gastrointestinal stromal tumour: Case report

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ABSTRACT

*Introduction:* GIST and NICTH are mesenchymal in origin however there are very few reports of GIST associated with NICTH which is a para neoplastic syndrome, generally diagnosed when a tumour induced hypoglycaemia is noted.

*Case presentation:* A 46 years old female with prime complain of awareness of a mass in the upper abdomen was admitted for evaluation and further management. Detailed investigation revealed the mass to be gastrointestinal stromal tumour. On the day of admission patient was found to be hypoglycaemic which didn't resolve even after 10% glucose infusion. A growth hormone releasing peptide-2 (GHRP-2) assay was carried out which showed an excessive reaction of basal growth hormone however corticotropin releasing hormone (CRH) tests were within normal limits. She was suspected to be Non Islet cell tumour hypoglycaemia (NICTH) and hypoglycaemia resolved upon administering dexamethasone. Later she underwent chemotherapy and surgical resection after which her blood sugar levels were within normal limits.

*Discussion:* Expression of big IGF-II on the surface of GIST be it metastatic or nonmetastatic can cause refractory hypoglycaemia and can be fatal if left untreated.

*Conclusion:* Clinicians should be aware of refractory hypoglycaemia in patients with large GIST's as glucocorticoid therapy may prove to be extremely useful and lifesaving even before considering any forms of definitive management of the tumour.

## 1. Introduction

Both GIST and NICTH are mesenchymal in origin however there are very few reports of GIST associated with NICTH. NICTH is a para neoplastic syndrome which is generally diagnosed when a tumour induced hypoglycaemia is noted [1,2]. Tumour induced hypoglycaemia is generally linked to the high molecular weight insulin growth factor II (IGF-II) which is also known as pro IGF-IIE(68–88) [2,3]. We did a PubMed search with keywords “GIST”, “NICTH” and were able to find only few such cases which were reported and we also noticed that all those cases were seen in metastatic GIST. So here in we report a unique case of nonmetastatic GISTs with recurrent hypoglycaemic episodes secondary to NICTH. The case report was realized according to international SCARE guidelines. [4]

## 2. Case report

A 46 year old woman presented to the gastroenterology out-patient department with complain of awareness of a mass in the upper abdomen for last one year. She denied any history of associated pain, bloating sensation, early satiety, jaundice, weight loss, fever. There was no history suggestive of altered bowel habits, blood in stool, nausea or vomiting. On probing she admitted feeling fatigued on doing any exertional work which was associated with dizziness. There was no recent travel history or contact with tuberculosis. Past medical history and family history were noncontributory. On examination pallor was seen with no evidence of icterus, clubbing, cyanosis, lymphadenopathy or edema. Vital signs were stable. Examination of cardiovascular system and respiratory system were within normal limits. On examination of the abdomen a nontender vague 5 cm × 5 cm intra-abdominal intra-

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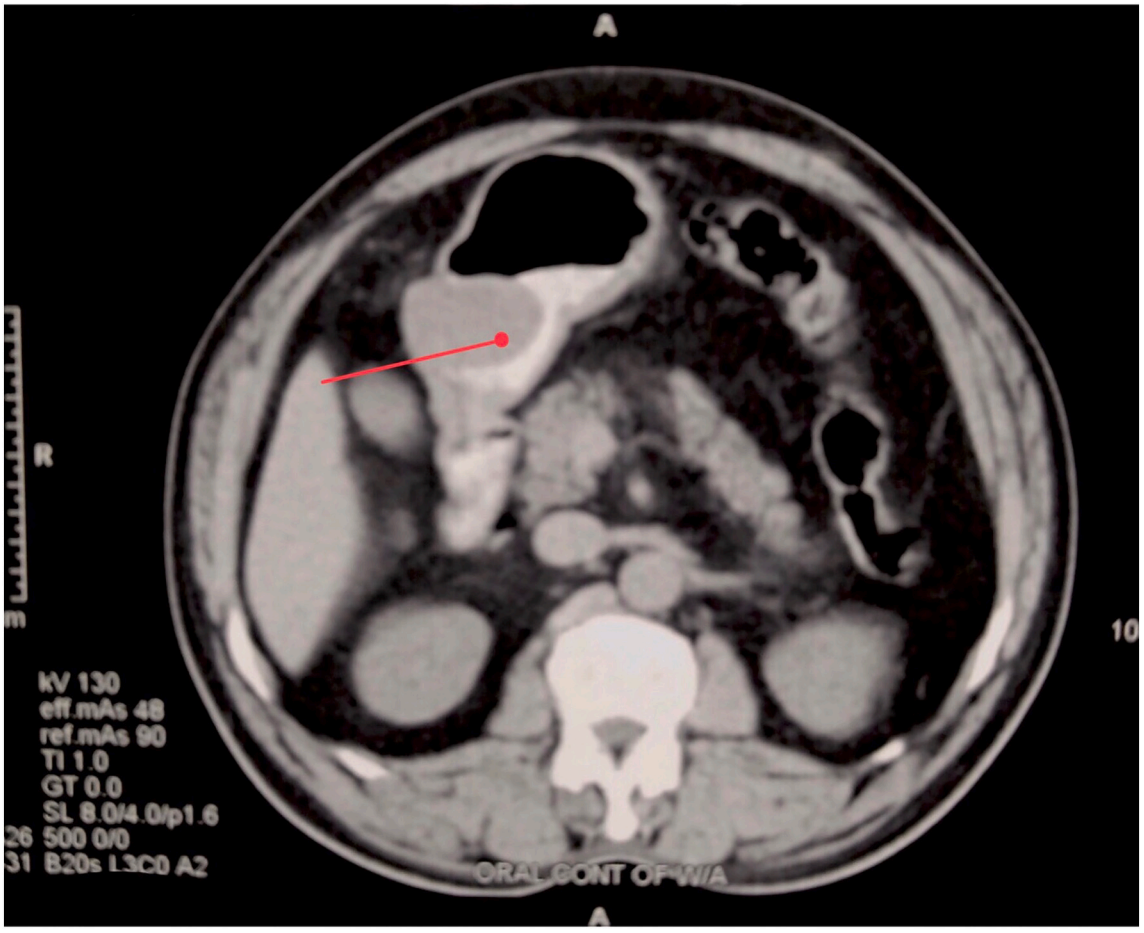


**Fig. 1.** CECT showing enhancing, soft tissue density, round shaped, endophytic mass in the antrum of stomach effacing the lumen (contrast column) medially.

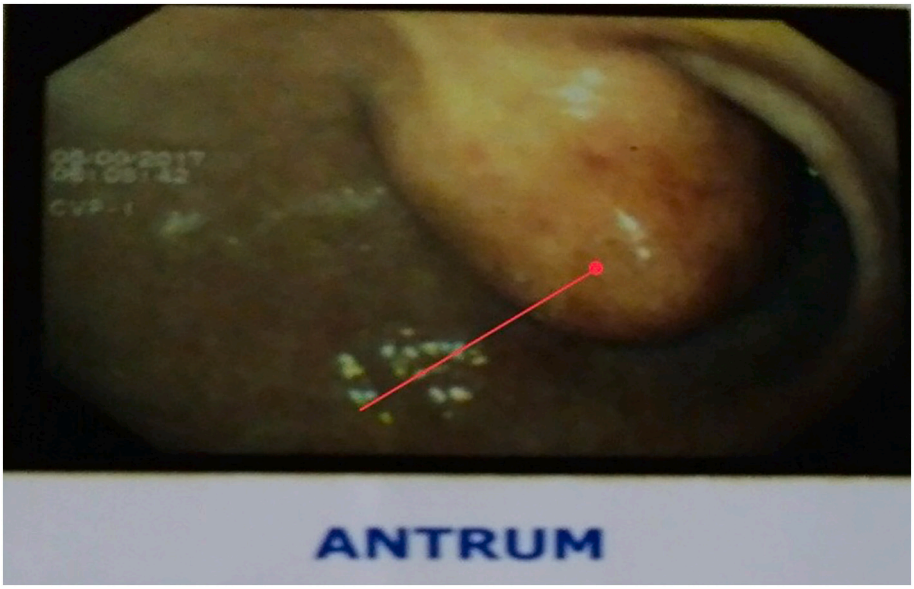


**Fig. 2.** Upper GI endoscopy showing a polypoidal lesion in the antrum of the stomach with broad base. Mucosa overlying the lesion is smooth indicating sessile.

peritoneal mass was felt in the epigastric and umbilical area. There was no visible gastric or intestinal peristalsis. No free fluid was felt. Bowel sounds were normal. Due to its long standing history and no other prominent clinical symptoms a differential diagnosis of mesenteric cyst; GIST and loculated tubercular ascites were considered. Routine laboratory investigation showed Haemoglobin- 8 g/dl; LFT and RFT profiles were within normal limits. Contrast enhanced computed tomography was advised (Fig. 1) which showed an enhancing, soft tissue density,

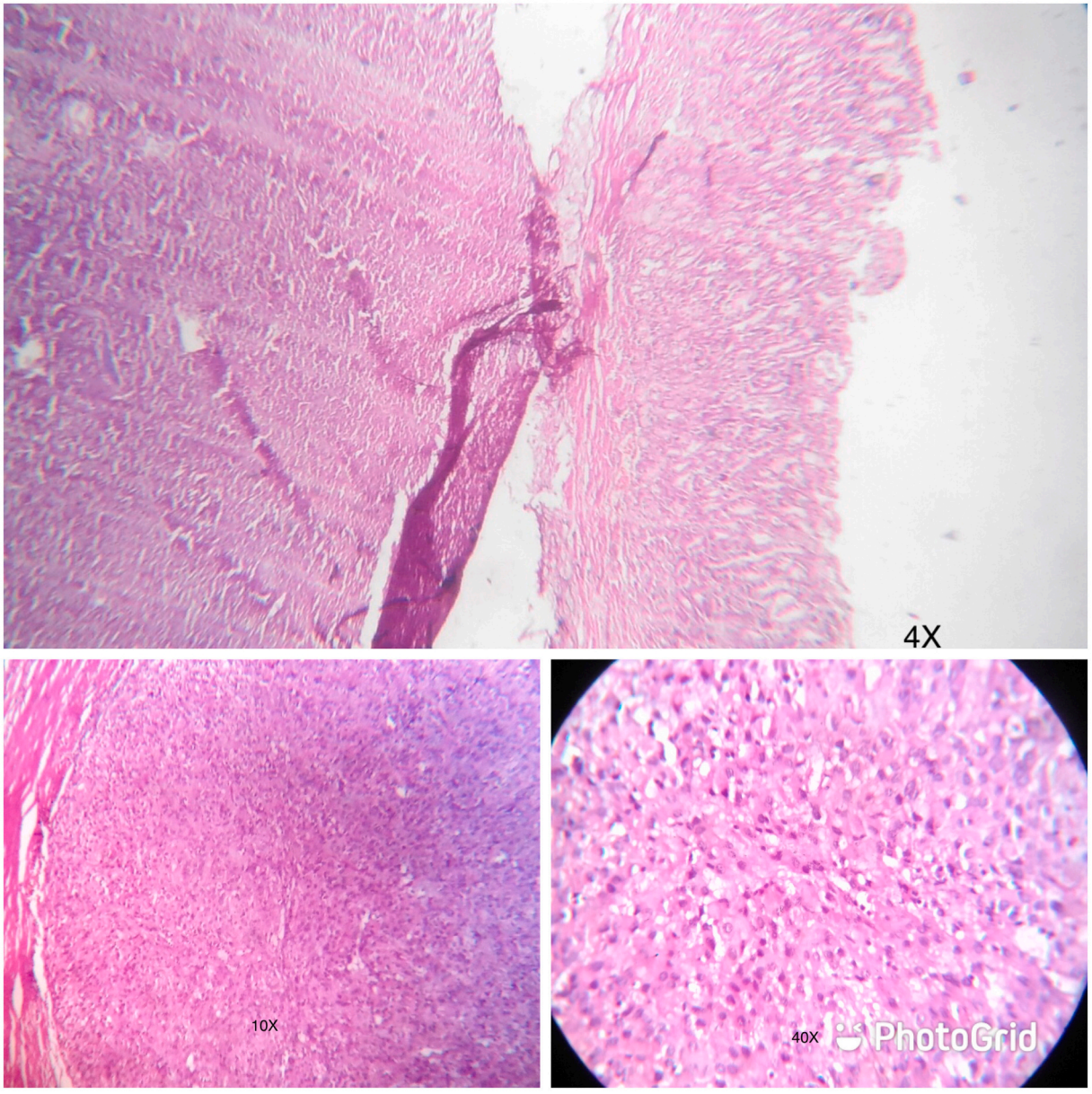


**Fig. 3.** H&E image at magnification 4X (top), 10X (bottom,left), 40X (bottom,right) showing features suggestive of epithelioid GIST.

round shaped, endophytic mass in the antrum of stomach effacing the lumen (contrast column) medially. The lesion did not have any extra-luminal component. No obvious necrosis or calcification was noted. No feature of gross gastric outlet obstruction seen. No adjacent lymph-adenopathy seen. A hypodense lesion was seen in right lobe of liver suggestive of hepatic cyst. Features were consistent with GIST in antrum of stomach. Furthermore an upper gastrointestinal tract endoscopy was done which showed (Fig. 2) a polypoidal lesion in the antrum of the stomach with broad base. Mucosa overlying the lesion was smooth indicating sessile polyp in the antrum of the stomach. Owing to the large, avascular nature of the tumour with no visible bleeding points and normal coagulation profile, biopsy was taken during endoscopy after which there was no evidence of bleed. Histo-pathological examination of the biopsy showed (Fig. 3) epitheloid GIST with moderate risk stratification based on size of tumour and mitotic activity. Immunohistochemistry of the sample showed CD117 positive (Fig. 4) confirming the diagnosis to be epitheloid GIST. Although we had kept EUS as a backup if the tissue diagnosis would have been noncontributory as endoscopic biopsy can sometimes miss the diagnosis of GIST as it is a submucosal lesion, which was not the case for us. On the day of admission her blood sugar profile was 35, 50, 80, 38, 55, 40, 80, 70 at 7:30, 10:00, 11:30, 14:00, 17:30, 20:00, 23:00 respectively. However hypoglycaemia persisted in spite of treatment with oral glucose and 10% continuous glucose infusion. Growth hormone releasing peptide-2 tests was conducted which showed low basal GH with an extensive reaction following which corticotropin releasing hormone(CRH) test was done which revealed normal corticotropic response (Table 1). serum C-peptide, insulin, IGF-I levels were suppressed. Therefore; she was suspected having NICTH. To confirm the diagnosis, big IGF-II was detected in her serum by Western blot analysis. Dexamethasone was administered at a doze of 1 mg/day which resolved the hypoglycaemia. Patient was considered for chemotherapy with Imatinib mesylate followed by surgical resection of the tumour. After informed consent; patient was taken up for open subtotal gastrectomy due to large size of the tumour and possibility of malignant GIST as refractory hypoglycaemic episodes though rarely encountered were mostly seen in malignant GISTs. Resected specimen (Fig. 5) was sent for histopathological examination which confirmed the diagnosis. Moreover immunohistochemistry

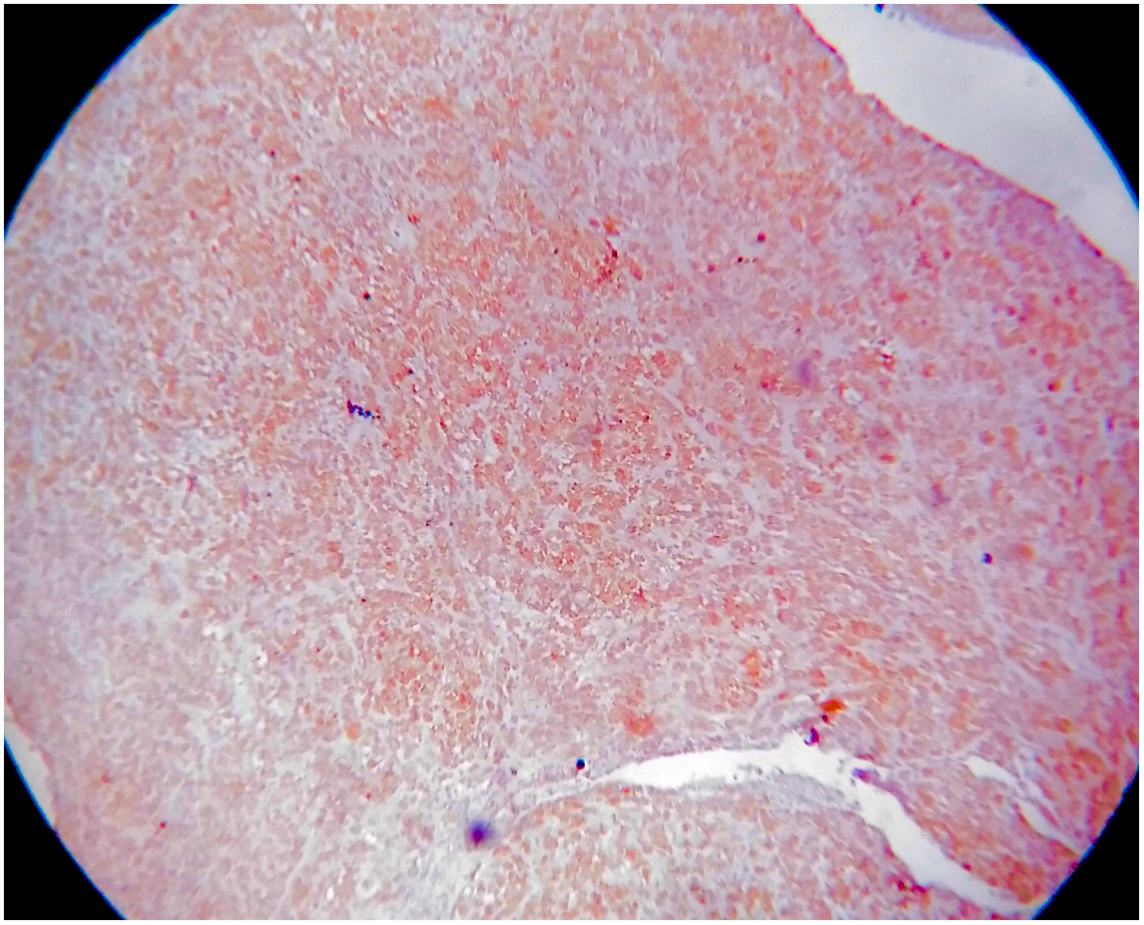

**Fig. 4.** IHC positive for CD 117.

**Table 1**
GHRP-2 stimulating test and CRH-stimulating test.

| GHRP-2 stimulating test | |
|---|---|
| TIME (min) | GH (ng/dl) |
| 0 | 0.08 |
| 30 | 17.6 |
| 60 | 36.9 |
| 90 | 36.1 |

| CRH-stimulating test | | |
|---|---|---|
| TIME (min) | ACTH (pg/mL) | GH (ng/mL) |
| 0 | 38.1 | 16.9 |
| 30 | 60.3 | 23.3 |
| 60 | 49.9 | 21.3 |
| 90 | 32.1 | 14.9 |
| 120 | 24.2 | 13.2 |

analysis revealed presence of IGF-II on tumour cells, hence the source of hypoglycaemic episodes were confirmed to be the tumour itself. Post-operative period was uneventful with random blood sugar values with in normal limit and there was disappearance of serum big IGF-II. She was discharged on post-operative day 10. At six months follow-up, she was tumour free with no other complaints.

## 3. Discussion

The case presented above shows two important things, first, clinicians should be aware of hypoglycemic episodes in patients with GIST as symptoms like fatigue, dizziness may be thought to be due to anaemia which is a known presentation of GIST and secondly glucocorticoid therapy can be helpful and life saving for patients who present with refractory hypoglycaemia secondary to GIST. These are mesenchymal tumours of the GIT. Immunohistochemistry plays an important role in distinguishing it from leiomyomas and neurogenic tumours. They generally originate from the interstitial cells of Cajal and can be both be metastatic as well as non metastatic. These tumours come up with a lot of symptoms such as abdominal pain, gastrointestinal bleeding, anaemia, palpable abdominal mass, dyspepsia, nausea, vomiting and obstruction, constipation, diarrhoea, swallowing difficulty and weight loss [5–10]. However, “vague abdominal discomfort” has been described by many authors as the prime complaint in 70% of patients diagnosed with GIST [6]. Asymptomatic GIST's generally pose a diagnostic challenge and is generally discovered accidentally by imaging modalities such as CT and endoscopy. Many patients are found pale and hence symptoms like easy fatiguability, drowsiness are attributed to anaemia secondary to GI bleeding. Hypoglycaemia is an important differential symptom that should be ruled out immediately at the onset of symptoms as these are life threatening conditions but can be treated easily once diagnosed. The total annual incidence of GIST has been reported in the range of 6.8 in USA to 14.5 in Sweden (cases per million) [1]. They generally occur in stomach (40%–70%) followed by small intestine (20%–40%) and less than 10% in oesophagus, colon and rectum [11–15]. Histopathologically GIST comprises of epitheloid and spindle shaped smooth muscle type cells. Pathological classification of GIST are done on the basis of Fletcher, Miettinen and modified Fletcher system [16].

In our case since hypoglycaemia didn't reduce with 10% glucose infusion and both IGF-I and insulin levels were supressed, IGF-I

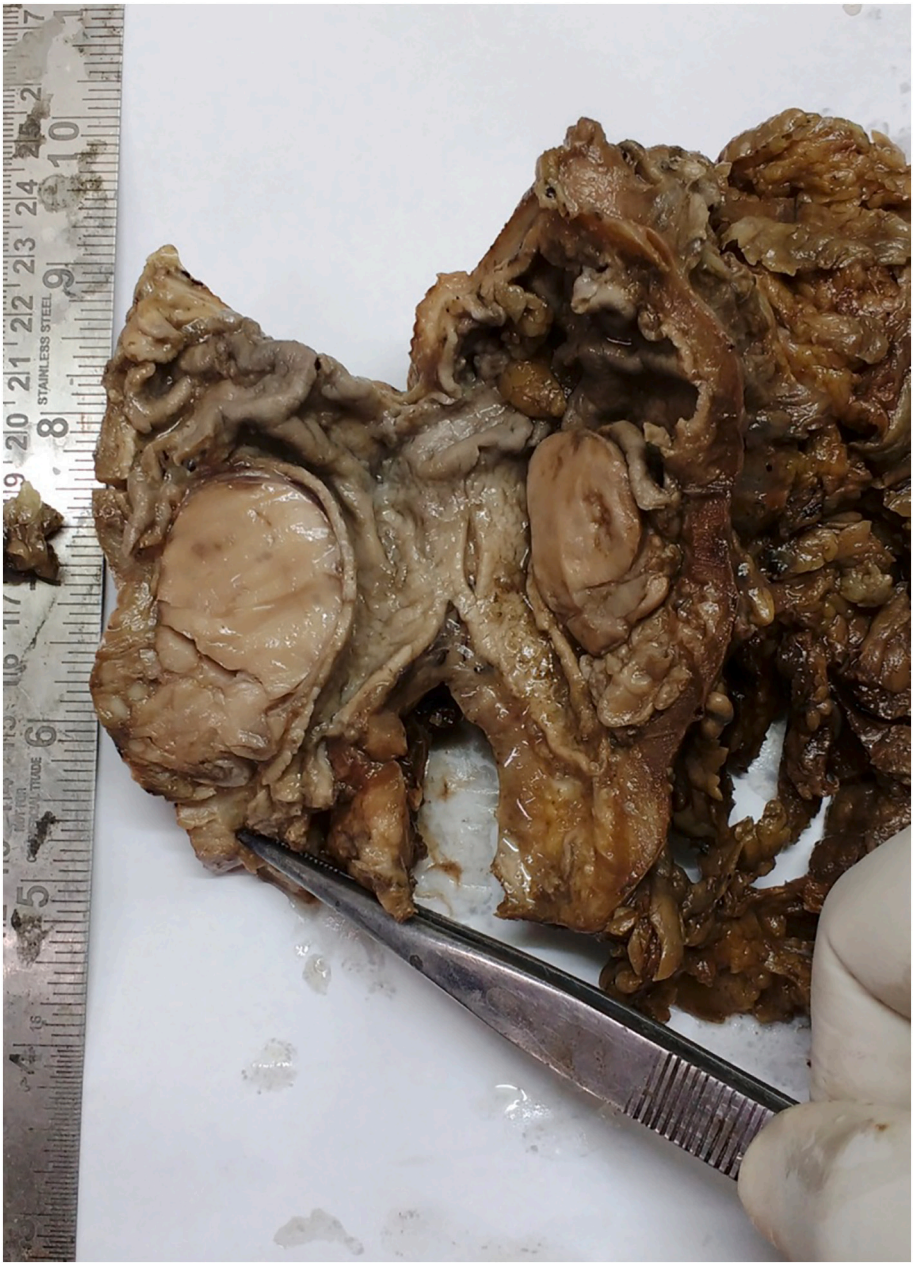


**Fig. 5.** Gross specimen post subtotal gastrectomy showing well encapsulated tumour in the antrum of stomach.

producing tumours were ruled out. Hypoglycaemia was reported as the presenting syndrome in 31 of 65 cases (48%) with presence of big IGF-II [17]. In our case other primary causes of hypoglycaemia is ruled out due to the presence of big IGF-II in serum and GIST nodules. In most of the cases, there has been disappearance of serum big-IGF II factors after removal of GIST tumour. Currently the most definitive way of diagnosing GISTs are by the immunostaining of the biopsy sample with the c-kit and using this as the diagnostic modality, a lot of leiomyosarcomas have been re-diagnosed as GISTs [18]. Rikhof et al. reported expression of big IGF-II on the surface of GIST can be detected both in-vitro as well as in-vivo, however the role of big IGF-II in GISTs is still unclear [19]. He also reported increased plasma levels of pro IGF-IIE(68–88) in cases of NICTH. Big IGF-II can thus be a useful clinical marker in the surveillance of GIST and can be a potential molecular target for treatment [3]. Presently, glucocorticoid treatment is currently done to ameliorate patients suffering from hypoglycaemia due to NICTH [1,2,20,21]. Teale et al. reported that secretion of big IGF-II can be suppressed by administering glucocorticoids [22]. Surgical resection, debulking or tumour embolisation can be considered as effective treatment options for confined, well defined non metastatic tumours. Metastatic and unresectable tumours can be cured by tyrosine kinase inhibitors with anti-neoplastic activity such as Imatinib, and is considered as the first line agent for treatment of GIST which has proven effective [23]. Surprisingly Hamberg et al. reported worsening of hypoglycaemia with NICTH by using Imatinib [24] which was not seen in our case. Hence a combination of glucocorticoid with Imatinib may prove useful. To our best knowledge, this is only case report of non-metastatic (localised) GIST associated with NICTH, and since paraneoplastic syndromes are associated with malignant tumours and we presented NICTH in a benign GIST, more case reports are required to understand the pathogenesis in finer details.

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Nil.

## Declaration of patient consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

## Author contribution

Arkadeep Dhali: Conception, design of the study, acquisition of the data, drafting the manuscript, final approval of the version to be submitted.

Sukanta Ray: Acquisition of the data, revising the manuscript, final approval of the version to be submitted.

Gopal Krishna Dhali: Acquisition of the data, final approval of the version to be submitted.

Ranajoy Ghosh: Acquisition of the data, final approval of the version to be submitted.

Avik Sarkar: Acquisition of the data, final approval of the version to be submitted.

## Registration of research studies

Not applicable.

## Ethical committee approval

Not required in our institution to publish anonymous case reports

## Guarantor

Dr. Gopal Krishna Dhali act as guarantor for the report and accept responsibility for the work.

## Provenance and peer review

Not commissioned, externally peer-reviewed.

## Declaration of competing interest

None declared.

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