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Case Report

Oncology Section

Paraneoplastic Hypoglycaemia: A Rare Manifestation of Pelvic Gastrointestinal Stromal Tumour

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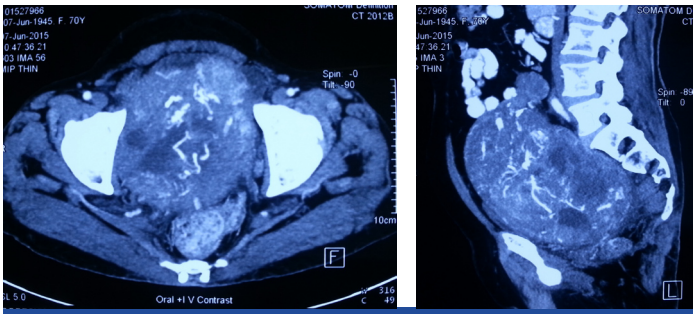
ABSTRACT

Non-Islet Cell Tumour Induced Hypoglycaemia (NICTH), presenting with recurrent fasting hypoglycaemia is a very rare paraneoplastic syndrome. It usually presents with large metastatic mesenchymal tumours. NICTH secondary to Gastrointestinal Stromal Tumour (GIST) is even rarer. Diagnosis of NICTH is based on the low serum insulin level, low serum concentrations of Insulin Like Growth Factor (IGF-I) and IGF binding protein- III (IGFBP-III) in combination with elevated concentrations of pro-IGF-II. Various Immunohistochemical (IHC) markers are integral to diagnosis of GIST namely 2-deoxyglucose-6-phosphate phosphatase -1(DOG-1), Cluster Differentiation 34 (CD 34), Cluster Differentiation 117 (CD117). The management requires prompt intravenous hydration and glucose infusions followed by surgical resection. We hereby, report a rare case of a 65-year-old female with intractable fasting hypoglycaemia due to overproduction of "big" insulin-like growth factor II diagnosed to have pelvic GIST and managed by Steroids and Imatinib.

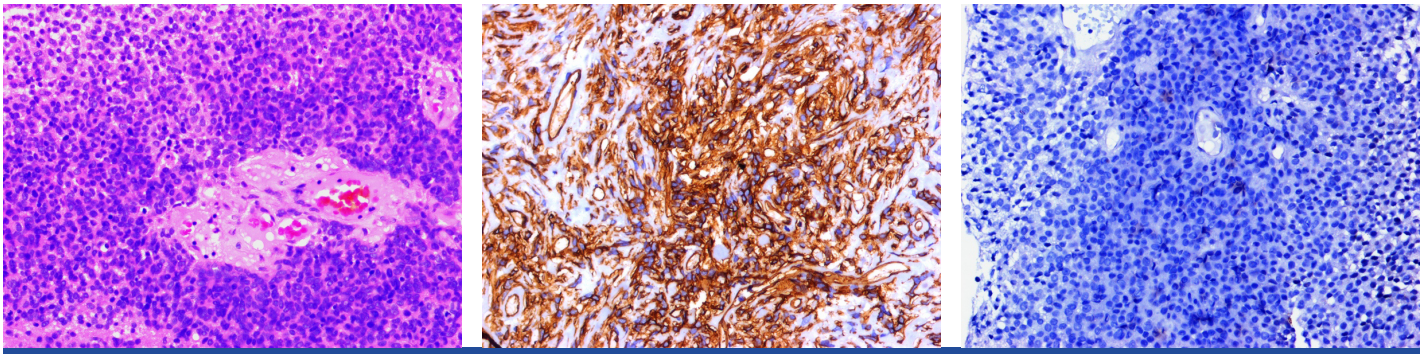
Keywords: Mesenchymal tumour, Non-islet cell, Paraneoplastic syndrome

CASE REPORT

A 65-year-old post-menopausal female with no medical comorbidities (diabetes/hypertension), presented to the Emergency Department with complaints of altered sensorium, preceded by generalized malaise and sweating for 2 hours. There was no history of chest pain, headache, respiratory distress, prior fainting episodes and trauma. On examination, she was cold and clammy with pulse rate of 130 per minute, blood pressure of 90/60mm of mercury in supine position and respiratory rate of 22/minute. Her pupils were normally reacting to light. There was no pallor and cyanosis. On systemic examination, she had an irregular large lump about 15x18 cm in size located in the hypogastruim, firm in consistency, non-tender with restricted mobility. She had a GCS score of 10/15, cranial nerve examination were normal. Her reflexes were sluggish with a normal plantar reflex. Her haematological investigations and serum biochemistry including liver and renal function tests and electrocardiogram were normal except for the presence of blood glucose levels of 23mg /dl. She was given 200ml of 25% dextrose following which she regained consciousness and sugar levels returned to normal. Her hypoglycaemia was intractable and repeatedly 25% glucose had to be administered to maintain euglycaemia. Her troponin, thyroid profile, cortisol, prolactin levels were normal. Contrast Inhanced Computed Tomography (CECT) abdomen showed a multi-lobulated heterogeneous abdomino-pelvic mass with areas of necrosis and calcifications [Table/Fig-1]. Right ureter was encased by the mass with evidence of mild hydronephrosis on the same side. The uterus was displaced superiorly by the mass and cervix was not visualized separately [Table/Fig-2]. There was no metastasis or any other space occupying lesion in the abdomen. CECT Brain did not show any evidence of stroke or space occupying lesion. USG guided biopsy was done which was consistent with the diagnosis of GIST (CD 34 positive, CD117 negative) [Table/Fig-3-5]. To delineate the cause of intractable hypoglycaemia, serum insulin was done which was 4mU/L, (normal 6-25) and C-peptide was 0.3nmol/L (normal 0.33-1.0). Serum proinsulin levels were 56.4 (normal < 18.8pmol/l). IGF levels could not be done due to laboratory limitations. Due to suppressed insulin levels and raised proinsulin levels, the diagnosis of IGF-II dependent Non-islet Cell Tumour induced Hypoglycaemia (NICTH), was considered. Due to poor general condition and inoperability of the tumour, Methylprednisolone was started and she was gradually weaned off from Dextrose infusions. Right ureter was stented. When she became stable, she was started on Imatinib 400 mg/day to which her symptoms and hypoglycaemic episodes responded.



[Table/Fig-1]: Axial CT image showing heterogeneous pelvic mass with areas of calcification; **[Table/Fig-2]:** Sagittal CT image showing pre-sacral involvement.



[Table/Fig-3]: Photomicrograph shows tumour cells in sheets with round hyperchromatic nuclei and moderate amount of eosinophilic cytoplasm. (H&E, x200); **[Table/Fig-4]:** Tumour cells show cytoplasmic positivity for CD 34. (Diaminobenzidine, x200); **[Table/Fig-5]:** Tumour cells are negative for CD 117. (Diaminobenzidine, x200).

DISCUSSION

GIST is the most common mesenchymal tumours of the gastrointestinal tract affecting stomach (60–70%), small intestine, rectum and colon. It usually occurs after the age of 50 with no sex predilection. They are usually asymptomatic until detected due to the appearance of symptoms related to mass effect such as obstruction, gastrointestinal bleeding or perforation. Rare clinical manifestations include hyperpigmentation, mastocytosis and hypoglycaemia (NICTH) [1,2]. The indexed case too presented with altered sensorium due to hypoglycaemia but its intractability and unusual cause made us to report it.

NICTH is a paraneoplastic syndrome presenting with recurrent hypoglycaemia, associated with secretion of incompletely processed precursors of Insulin – like Growth Factors (IGF) by the tumour in the circulatory system. It tends to present in large or metastatic tumours, and can appear at any time in the natural history of the disease. The incidence of NICTH is thought to be one fourth of functional insulinomas (1 case of NICTH per million people-years) [2]. NICTH usually occurs with tumours of mesenchymal origin like fibromas, fibro sarcomas, leiomyosarcoma, solitary fibrous tumour, haemangiopericytoma but may also present with carcinoid, myelomas, lymphomas, hepatocellular, and colorectal carcinomas. Hypoglycaemia in NICTH is due to the suppression of Growth Hormone (GH) biosynthesis, overproduction of incompletely processed (IGF)-II, resulting in stimulation of the insulin receptors, increased glucose utilization and inhibition of glucose release from the liver. The net result is continued glucose utilization by skeletal muscle and inhibition of glucose release, glycogenolysis, and gluconeogenesis in the liver. Diagnosis of NICTH is based on the low serum insulin level, low serum concentrations of IGF-I and IGF Binding Protein- III (IGFBPIII) in combination with elevated concentrations of pro-IGF-II [3]. However, not all cases of NICTH have consistent findings. NICTH secondary to "big" IGF II is difficult to confirm because laboratory tests are not readily available for their assessment. Increased levels of IGF2-mRNA can be detected using northern blotting of tumour tissues [4]. IHC staining for KIT (CD117) is integral to the diagnosis of GIST, nearly 90% of GIST sharbors activating mutations in the KIT receptor tyrosine kinase gene. The tumour originates from the interstitial cells of Cajal and unregulated activation of KIT cause their proliferation. It has been found that specific KIT mutations serves as both prognostic and predictive marker in GIST of which exon 11 (79%) and exon 9 (11%) is the most common [5]. Exon 11 mutations serve as good prognostic and positive predictive marker for GIST; whereas, exon 9 and Platelet derived growth factor (Kit negative) serves as negative marker for both [6]. Imatinib is the drug of choice for GIST until secondary resistance develops. Sunitinib has recently been approved as second line for patients who fail Imatinib therapy; Rogerafinib or re-challenge with Imatinib can be used as third line with additional small molecule inhibitors are in the pipeline [6]. A swift intervention in terms of intravenous hydration and glucose infusions is important for the management of patients with NICTH [7]. Surgical resection remains the most rapid and cost-effective therapy to normalize glucose metabolism as soon as the patient becomes stable. Selective embolization and radiofrequency ablation also help in relieving hypoglycaemia. However, one should be cautious, as this may potentially result in greater circulating "big" IGF II due to rapid necrosis and resultant hypoglycaemia. In other cases of NICTH, low dose steroids and growth hormone have allowed for palliative weaning from intravenous glucose [7].

CONCLUSION

Optimal management of GIST-induced hypoglycaemia requires a multi-disciplinary team approach. Surgical resection is the treatment of choice to obtain immediate relief from the symptom. Imatinib or combinations of glucocorticoids and growth hormone can be used in symptomatic hypoglycaemia. Thus, we presented this case to remind clinicians that if an unusual clinical course of hypoglycaemia is found in patients who have history of progressive malignant tumour, especially involving GIST, NICTH should be included in the list of possible of differential diagnosis.

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