Paraneoplastic hyperinsulinism and secondary hypoglycaemia in a patient with advanced colon cancer: A rare association

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Abstract
We review the case of a 74-year-old patient with advanced colon cancer who suffered recurrent bouts of hypoglycaemia. A state of inappropriate, non-suppressed hyperinsulinism in the presence of severe hypoglycaemia was diagnosed. We finally discuss the known mechanisms behind fasting hyperglycaemia in patients with advanced cancer, the diagnosis, and possible treatments of this rare paraneoplastic endocrine complication.

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Key words: Hypoglycaemia; Colon cancer; Paraneoplastic; Hyperinsulinism; Tumour markers

CASE REPORT

A 74-year-old male patient was diagnosed in September 2004 with a sigmoid cancer with advanced hepatic and pulmonary metastases. He had no previous medical history of interest. The primary tumour was surgically removed. The pathologic study showed a moderately differentiated adenocarcinoma; the TNM staging was pT4 N2 (12/15) M1, stage IV. After surgery, his performance status (PS) was 1. There were no baseline laboratory abnormalities. His CEA and CA 19.9 levels were 270.9 ng/mL and 1257.3 UI/mL, respectively.

Between November 2004 and April 2005, he received 1st line chemotherapy with 12 fortnightly cycles of infusional 5-fluorouracil and oxaliplatin (FOLFOX regimen). A radiologically stable disease was achieved after the 6th and 12th infusion, with a lowering of the CEA and CA19.9 levels. Overall tolerance to chemotherapy was good; however, treatment was finally stopped due to persistent grade 2 chronic neurotoxicity (CTC version 3) secondary to oxaliplatin. At that moment, he began follow-ups in our clinic.

In July 2005, the patient suffered a loss of consciousness in the early hours of the morning. The capillary blood glucose at that moment was low (45 mg/dL) and he was brought to the Emergency Room (ER). There were no other basic laboratory abnormalities. The electrocardiogram was normal, as was a CT brain scan. With further questioning, the patient referred in the last weeks similar episodes of poor sleep, frequent nightmares, dizziness and blurred vision, although with no loss of consciousness, in the early hours of the morning, which improved with the ingestion of food. The patient had also gained weight in the last weeks, as he had a craving for sweet foods; he also had learnt to avoid these episodes of dizziness during the day with the increased food ingestion.

The patient was admitted for further study. His PS was 2 and it had deteriorated in the last few weeks. He was overweight, although there were signs of muscular atrophy. There were signs of peripheral oedema and ascitis and a

INTRODUCTION
Non-islet cell tumour hypoglycaemia (NICTH) is a rare association between spontaneous hypoglycaemia and tumours derived from tissues other than the pancreatic islets[1]. It was initially associated with abdominal soft tissue sarcomas, although other tumour types have been described. The most consistent finding is the overproduction of insulin or especially insulin-like growth factors by the tumour. We review the case of a patient with a sigmoid carcinoma with ectopic production of insulin and secondary hypoglycaemia and the clinical diagnosis and management of this rare condition.
palpable hepatomegaly of 4 cm of size. A more complete laboratory study only showed mild anemia (hemoglobin of 10.7 g/dL) and hyperalbuninemia (serum albumin of 2.2 g/dL), with no ionic abnormalities. The CEA and CA19.9 levels had risen (448.2 ng/mL and 2155.9 UI/mL, respectively). A CT scan showed hepatic and pulmonary progression of disease; there were also signs of peritoneal carcinomatosis and ascitis and a sigmoid mass.

During his admission, the patient suffered recurrent bouts of hypoglycemia in the early morning hours which needed the use of nocturnal intravenous 10% glucose hypertonic fluid for adequate control. No thyroid or adrenal axis abnormalities were found.

An overnight fasting test was performed under close medical supervision. It was stopped at 6:00 am when hypoglycemic symptoms appeared. In that moment, the glucose level was 20 mg/dL, the insulin level was 15.5 μU/mL (not suppressed), the C-peptide was 5.61 ng/mL (elevated) and IGF-I was less than 2 ng/mL (suppressed). All these data were compatible with fasting hypoglycemia secondary to hyperinsulinism. Neither a pancreatic arterial and venous-phase CT scan or an octeotride scan revealed signs of a primary pancreatic β-cell tumour.

Diazoxide was begun, which partially improved the hypoglycemia and the need for hypertonic fluids, at the cost of worsening of the peripheral oedemas. Due to the paraneoplastic nature of the hypoglycemia, 2nd line chemotherapy was begun with infusional 5-FU and irinotecan (FOLFIRI regimen) and a first infusion was given. However, the patients’ general state quickly deteriorated and an intestinal occlusion secondary to the peritoneal carcinomatosis developed, which did not improve with medical treatment. A multorgan failure appeared and the patient died 3 wk after the original admission. The patients’ family refused an autopsy.

**DISCUSSION**

NICTH is a rare clinical entity. In almost half of cases it has been linked to large pleural or abdominal mesenchymal tumours[1-3], retroperitoneal fibrosarcoma being the classic prototype. Other tumour types implicated have been hepatocarcinomas, adrenal carcinomas, and in a few cases gastrointestinal tumours, genitourinary tumours and lymphomas[4-8]. In many cases instances the tumour is already known to be present, usually in an advanced stage[9]. However, diagnosis can be difficult in those cases where it is the first clinical manifestation.

The pathogenesis of hypoglycemia in NICTH may involve a variety of mechanisms, including excessive consumption of glucose by what is typically a large tumour, inadequate production of counter regulatory hormones, such as growth hormone or cortisol, or ectopic or abnormal secretion of insulin or insulin-like growth factor-2 (IGF-II) and IGF-binding proteins. This last mechanism seems to be the most frequent and best characterized in patients with typical NICTH[1-7]. Insulin secretion by the non-β-cell tumour, as in our case, is extremely rare and most cases published are secondary to secretion of an incompletely processed IGF-II by the tumour (“big IGF-II”), which can be measured with specialized assays) which acts as an insulin-like factor in the insulin receptors, causing hypoglycemia[8]. The fasting suppression state can differentiate between both conditions, as in the setting of hypoglycemia, insulin levels will be non-suppressed in the former and suppressed in the latter. In both cases, however, IGF-I levels will be suppressed, which can be a useful marker in these patients[9].

The clinical presentation is usually severe fasting hypoglycemia, which is persistent and requires intravenous glucose administration for reversal. Because the onset of fasting hypoglycemia is often gradual, autonomic signs are minimal or absent in most cases and neuroglycopenic symptoms predominate. They are most common in the early morning, after the overnight fast. The differential diagnosis includes all other conditions which can produce fasting hypoglycemia in adults and includes renal or hepatic failure, adrenal insufficiency, sepsis, β-cell pancreatic tumours, ethanol ingestion or drugs (usually insulin or sulfonylureas)[9,10]. Most are easily ruled out and the differential usually only includes β-cell pancreatic tumours, adrenal insufficiency or factitious hypoglycemia secondary to exogenous administration of insulin or sulfonylureas[10].

In our case, there were no adrenal axis abnormalities. The patient was in close medical supervision, with no contact with hypoglycemic drugs and so factitious hypoglycemia was ruled out. An overnight fast revealed a severe hypoglycemia, alongside a non-suppressed insulin and an elevated C-protein, which seemed to show an autonomous secretion of insulin. However, there were no radiological signs of a concomitant β-cell pancreatic tumour. The hypoglycemia also behaved like a paraneoplastic phenomena; its appearance was quite sudden and it coincided with the tumour progression, both radiologically and in the elevation of the tumour markers.

Treatment of this infrequent condition can be difficult. These patients often require continuous glucose infusions to control their symptoms. In some cases, diazoxide, a potent inhibitor of insulin secretion, has been useful[10]. Debulking surgery may bring relief to the hypoglycemia, especially in those with slow-growing mesenchymal tumours[1,3][11]. Specific treatment should be instituted if possible (e.g., imatinib in gastrointestinal stromal tumours)[12]. In most cases, however, the outcome is often poor due to the size and advanced stage of the tumour.

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