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# Extreme Hypoglycaemia in Anaplastic Large Cell Lymphoma

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## ABSTRACT

*Introduction:* Hypoglycaemia associated with non-islet cell tumours (NICTH) is a rare entity in patients with extra-pancreatic malignancies, mostly attributed to large mesenchymal or epithelial tumours. Anaplastic large cell lymphoma has not previously been associated with NICTH, making this the first publication of such a report.

*Patient and methods:* A 22-year-old, non-diabetic patient was admitted to our department with malaise, itching, night sweats and weight loss. Serum glucose levels at presentation were extremely low, reaching 3 mg/dl at the lowest. Further investigations revealed undetectable blood insulin and C-peptide levels, together with low IGF-1 (34 ng/ml) levels. Inguinal lymph node biopsy showed anaplastic large cell lymphoma, and bone marrow biopsy along with supporting blood tests revealed haemophagocytic lymphohistiocytosis.

*Discussion:* In conjunction with an adequate hyperglycaemic response to intravenous glucagon, all of the above findings indicate hypoglycaemia as a result of overproduction of high molecular weight IGF-2 precursor protein, generally referred to as 'Big IGF-2'. Large solid tumours can occasionally produce loosely bound or free Big IGF-2 molecules which circulate throughout the plasma and bind to insulin as well as IGF receptors, thus increasing glucose intake by body tissues, decreasing the release of glucose to the bloodstream by the liver and causing feedback suppression of insulin, IGF-1 and growth hormone production. Therefore, it is exceptional to find Big IGF-2-related hypoglycaemia in non-solid tumours. Our case shows that, although extremely uncommon, rare instances of NICTH can be attributed to the production of Big IGF-2 in non-solid malignancies including anaplastic large cell lymphoma.

## LEARNING POINTS

- Although extremely rarely, haematological malignancies can produce non-islet cell tumours (NICTH) as a result of IGF-2 and Big IGF-2 secretion.
- Insulin, C-peptide and IGF-1 levels may be sufficient to diagnose NICTH.

## KEYWORDS

NICTH, ALCL, hypoglycaemia, Big IGF-2, IGF-2

## BACKGROUND

Tumour-associated hypoglycaemia is mainly attributed to insulinomas. However, the second most common tumour-associated hypoglycaemia is a rare paraneoplastic phenomenon called non-islet cell tumour hypoglycaemia (NICTH). The first description of hypoglycaemia in the setting of tumoural disease was in 1929, in a patient with hepatocellular carcinoma[1]. NICTH, in most cases, is associated with either overproduction of insulin-like growth factor 2 (IGF-2), abnormal production of pro-IGF-2 (Big IGF-2) or both, first described by Daughaday et al. in 1988[2]. Being a rare clinical entity, the true incidence of NICTH is not known, but it is considered to be much less frequent than

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hypoglycaemia from insulinomas. The most common cancers causing NICTH are tumours of the gastrointestinal tract, lungs, pancreas, adrenal and ovary.

Some cases of hypoglycaemia in conjunction with lymphoma have been reported, suggesting different mechanisms such as increased glucose consumption by the tumour mass and/or its metastases and autoantibodies to the insulin receptor[3]. Only two cases of IGF-2-related hypoglycaemia in the setting of lymphoma have been described, neither of which was associated with anaplastic large cell lymphoma (ALCL).

## CASE REPORT

A 22-year-old man was admitted to our internal medicine ward with a history of general weakness for several months, accompanied by night sweats, sub-febrile fever, itching and weight loss. A few weeks before his admission, the patient had noticed a left inguinal mass on self-examination. Family history included a mother with neurofibromatosis type I. Vital signs were steady except for sinus tachycardia of 140 bpm. His physical examination revealed extensive skin abrasions, appearing as excoriations; a rigid left inguinal mass was palpable, measuring around 2×4 cm. Complete blood count included 45,000 white blood cells (per µl) (predominantly neutrophils), haemoglobin of 6.7 mg/dl and 600,000 platelets (per µl). Serum glucose levels were 74 mg/dl (normal 70–100) and rapidly dropped to values as low as 3 mg/dl. Low glucose levels were also confirmed with a finger stick glucose monitoring device. During this episode, the patient was shaking, sweating and ultimately exhibited a reduced level of consciousness. Investigation of the hypoglycaemia revealed extremely low levels of insulin (0.2 mIU/ml; normal 3–25) and C-peptide (<0.1 ng/ml; normal 0.9–7.1), as well as low IGF-1 levels (34 ng/ml; normal levels adjusted for age and sex: 127–364). Cortisol morning levels were within normal range (480 nmol/l; normal 138–635) The patient regained consciousness after being treated with continuous intravenous infusions containing 10% dextrose solutions, barely maintaining blood glucose levels in an appropriate range. Intramuscular injection of glucagon during a hypoglycaemic episode (30 mg/dl) increased blood glucose levels to 100 mg/dl. Chest and abdominal CTA revealed several small retroperitoneal lymph nodes. Elevated sIL2R and ferritin levels together with bone marrow biopsy produced findings matching those of haemophagocytic lymphohistiocytosis syndrome (HLH), so the HLH-94 treatment protocol was started. Simultaneously, the patient underwent inguinal mass biopsy, revealing findings indicating anaplastic large cell lymphoma, and so brentuximab was added to the treatment. Despite rapid diagnosis and treatment, the patient's status continued to deteriorate, leading to multi-organ failure and death.

## DISCUSSION

Abnormally reduced IGF-1 levels in a patient with hypoinsulinaemic hypoglycaemia strongly suggest the diagnosis of NICTH. In NICTH patients, as in our case, serum levels of insulin, C-peptide and IGF-1 are usually decreased or undetectable. Serum levels of total IGF-2 can, however, be increased, decreased or normal, making a diagnosis of NICTH relying on IGF-2 levels alone unreliable as various molecules such as Big IGF-2 (immature IGF-2) and mature IGF-2 are included under the label 'total IGF-2'. While in healthy subjects Big IGF-2 constitute 10–20% of total IGF-2, in NICTH Big IGF-2 levels can be as high as 60–70% of total IGF-2[4]. IGF-2 levels are frequently within the normal range in NICTH, making differentiation between Big IGF-2 and total IGF-2 difficult as Big IGF-2 assays are not commercially available; however, in patients with tumour-associated hypoinsulinaemic hypoglycaemia, an IGF-2:IGF-1 ratio of >10 is considered to be clinically significant, and can be used to make the diagnosis of NICTH.

Although IGF-2 levels in the blood, bone marrow or biopsy specimen were not obtained, we presume that this case of hypoglycaemia can be attributed to NICTH because of the lack of any other hypoglycaemia-associated mechanisms (such as insulinoma, sepsis, liver or adrenal insufficiency), and the presence of low insulin, C-peptide and IGF-1 levels. Moreover, the response to glucagon and initial treatment of ALCL resulting in the maintenance of a euglycaemic state supports the diagnosis. As regards lymphoma, Gorden et al.[5] investigated seven patients with hypoglycaemia and lymphoma for plasma 'IGF like material' levels (a material now known to be identical with IGF-2). These levels were low compared both with a normal reference population and with patients with other types of tumour-producing NICTH. Interestingly, some cases of hypoglycaemia in Hodgkin's disease revealed suppressed levels of plasma insulin, C-peptide and proinsulin while IGF-1, IGF-2 and the IGF-2:IGF-1 ratio were normal. This actually makes our case more unusual, as insulin, C-peptide and IGF-1 levels were all low, emphasizing the reasonable association with NICTH and IGF-2-related hypoglycaemia.

In conclusion, although rare, NICTH should be considered a possible diagnosis in patients with hypoglycaemia. In such settings, physicians should not overlook the possibility of haematological or non-solid tumour disease.

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## REFERENCES

1. Nadler W. Hepatogenic hypoglycemia associated with primary liver carcinoma. *Arch Intern Med* 1929;**44**:700.
2. Daughaday W, Emanuele M, Brooks M, Barbato A, Kapadia M, Rotwein P. Synthesis and secretion of insulin-like growth factor II by a leiomyosarcoma with associated hypoglycemia. *N Engl J Med* 1988;**319**:1434–1440.
3. Marks V, Teale JD. Tumours producing hypoglycaemia. *Endocr Relat Cancer* 1998;**5**:111–129.
4. Dutta P, Aggarwal A, Gogate Y, Nahar U, Shah V, Singla M, et al. Non-islet cell tumor-induced hypoglycemia: a report of five cases and brief review of the literature. *Endocrinol Diabetes Metab Case Rep* 2013;**2013**:130046.
5. Gorden P, Hendricks C, Kahn C, Megyesi K, Roth J. Hypoglycemia associated with non-islet-cell tumor and insulin-like growth factors. *N Engl J Med* 1981;**305**:1452–1455.

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