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Case Report

Unusual presentation of malignant ovarian endometrioid carcinoma with hypoglycaemic seizures: a case report

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Introduction

Recurrent hypoglycaemic episodes adversely impact overall well-being and quality of life. Severe untreated episodes may be life threatening. Hypoglycaemia, in the context of malignancy, is an infrequent occurrence and can be attributed to various factors including excessive production of insulin-like growth factor 2 (IGF2), insulin, somatostatin or glucagon-like peptide 1 as a paraneoplastic phenomenon or the presence of autoantibodies against insulin or its receptors or extensive metastases affecting the liver or adrenal glands leading to impaired glucose regulation [1]. Hypoglycaemia may also result from inherent glucose uptake by tumour cells, which is the basis of positron emission tomography (PET) scanning. This case report presents the clinical details and management of a 58-year-old, post-menopausal woman with recurrent hypoglycaemic episodes and a subsequent diagnosis of high-grade, metastatic, endometrioid carcinoma of the ovary. The report highlights the unusual presentation of paraneoplastic hypoglycaemia as a result of IGF2 secretion and emphasizes the importance of considering less common causes of hypoglycaemia in clinical practice. It expands our understanding of the diverse clinical presentations of ovarian malignancies. Additionally, it discusses the diagnostic findings, surgical intervention, and histopathological characteristics of the tumor, providing valuable insights into the management of this rare and challenging condition. To the best of our knowledge this is the first reported case of such an association with endometrioid ovarian malignancy.

Case report

We present the case of a 58-year-old, post-menopausal woman who was found by her family members in a drowsy and convulsive state in the morning. Upon arrival at the hospital's emergency unit, she was immediately placed in the left lateral position and connected to oxygen via a face mask. The Glasgow coma scale (GCS) on admission was

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11/15. A point-of-care capillary blood sugar (CBS) test revealed hypoglycaemia with a reading of 33 mg/dL (1.8 mmol/L). Her seizures and drowsy state improved rapidly following the administration of four intravenous boluses of 25% dextrose and a continuous dextrose infusion, thereafter. She had no significant past medical or family history. She did not recall waking up during that night with symptoms of hypoglycaemia and was unaware of her presentation with drowsiness and seizures. On the previous night, she had consumed her usual dinner and gone to bed without experiencing any warning symptoms. However, for three mornings preceding her presentation, she experienced symptoms of hunger, diaphoresis and tremors upon waking up, which had resolved after consuming a sugary beverage. She denied taking any medications or herbal products that could induce hypoglycaemia. She was not following a calorie-restricted diet and did not report any change in weight. She was nulliparous and had experienced sporadic, post-menopausal vaginal bleeding during the previous six months, along with gradually worsening lower abdominal fullness. However, she did not report any abdominal pain or changes in bowel or urinary symptoms.

On examination, the patient was found to be overweight, with a BMI of 26 kg/m^2. Her vital signs were within normal limits, including a pulse rate of 100 beats per minute, blood pressure of 140/95 mmHg, oxygen saturation of 98% on room air and a respiratory rate of 18 breaths per minute. She appeared pale and had hirsutism, but there were no signs of jaundice, lymphadenopathy or oedema. Abdominal and vaginal examination revealed a large, irregular, smooth, non-tender pelvic mass with free fluid in the flanks. Additionally, there was dullness to percussion and absent air entry in the right lung base, consistent with a moderate pleural effusion. The rest of the examination was unremarkable.

The patient was transferred to a general medical unit for further care, where her vital signs and random blood sugar levels were closely monitored. She experienced recurrent symptomatic hypoglycaemic episodes during periods of fast, with low CBS values ranging from 35 to 60 mg/dL being reported. Her 2-hour postprandial values ranged from 140 to 151 mg/dL. Her HbA1c level was 5.1% (32 mmol/mol).

Table 1 provides the results of the various blood investigations performed. The IGF2 levels were raised, whereas levels of IGF1, insulin, c-peptide and serum ketone bodies (beta hydroxyl butyrate) were suppressed. The patient's serum potassium level was low at 2.84 mmol/L but no acute hypokalaemic electrocardiographic changes were observed. The potassium level improved to 3.6 mmol/L with oral potassium chloride supplementation. Haematological investigations revealed anaemia with haemoglobin level of 9.8 g/dL and features of iron deficiency, whereas the platelet and white cell counts were normal. These findings were attributed to the per vaginal blood loss. A chest X-ray showed a right-sided effusion, the diagnostic analysis of which revealed a clear transudate with few cells, a protein level of 1.83 g/L, and a glucose level of 54 mg/dL. An abdomino-pelvic ultrasound showed a homogeneous, lobulated, solid and cystic, well vascularized pelvic adnexal mass extending up to the level of the umbilicus and moderate ascites.

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Table 1. Blood investigations performed during presentation.

Investigation (Unit)	Patient's value	Normal range
Serum ketone bodies (mmol/L)	undetectable	<0.6
Serum insulin level when blood sugar was 35 mg/dL with symptoms (IU/mL)	0.2	2.6 – 24.9
C-peptide levels when blood sugar was 35 mg/dL (ng/mL)	0.1	0.9 – 7.1
IGF1 level (ng/ml)	< 1	52 – 233
IGF2 level (ng/ml)	900	521–873
HbA1c	5.1 % (32 mmol/mol).	4 – 5.6 % (20 – 38 mmol/mol)
9 am cortisol (mmol/L)	456	123 – 626
TSH	1.34	0.4 - 4.6
ESR (mm/hour)	20	< 30
Serum creatinine (µmol/L)	35.7	61.9 to 114.9
Serum sodium (mmol/L)	140	135 – 145
Serum potassium (mmol/L)	2.84	3.5 – 4.5
Serum calcium (mmol/L)	2.08	2.1 – 2.5
Serum magnesium (mmol/L)	0.72	0.7 – 1.0
Serum phosphorus (mmol/L)	0.77	0.81 – 1.45
Urine potassium/ creatinine ratio	3.21	<1.5
Alanine transaminase (U/L)	19	4 – 36
Alkaline phosphatase (U/L)	78	44 – 147
Serum albumin (g/L)	4.0	3 – 5
INR	1.1	
Blood CA-125 (IU/L)	1140	< 35

The patient was evaluated by the specialist endocrinology and gynaecology teams. On the 7th day of hospitalization, she underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy under general anaesthesia. Intraoperative monitoring revealed hypoglycaemia, which required continuous intravenous dextrose infusion. A large, irregular, solid, right ovarian mass, measuring 19 x 17 x 17 cm, with necrotic areas, adherent to the adjacent sigmoid colon, and omental deposits were identified (Figure 1).

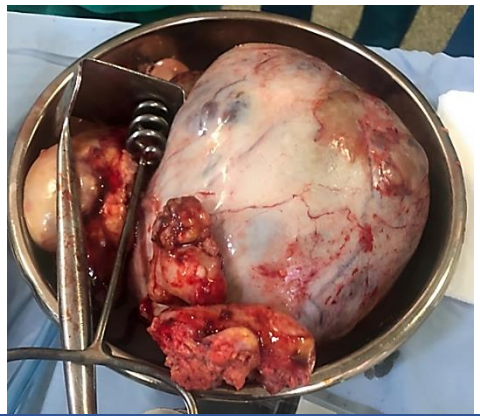

Figure 1. Macroscopic appearance of large right ovarian mass

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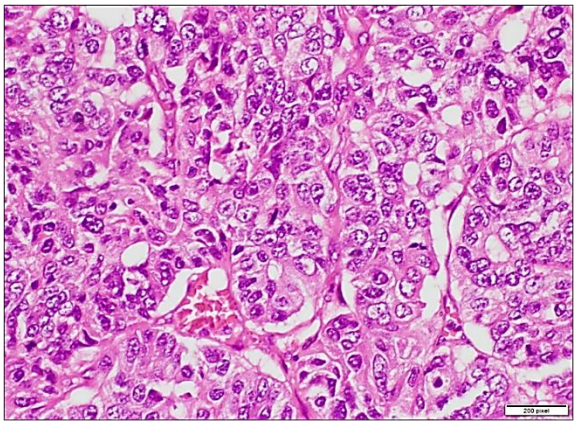
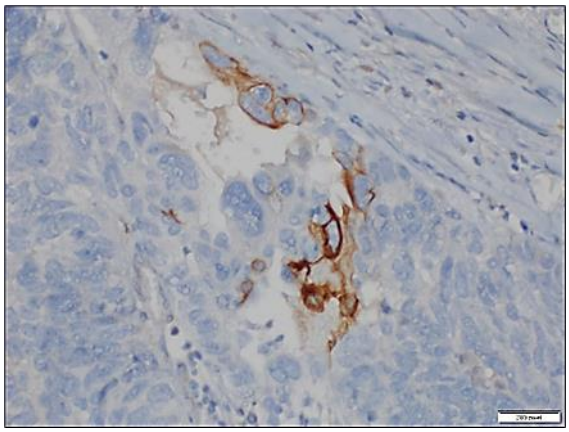
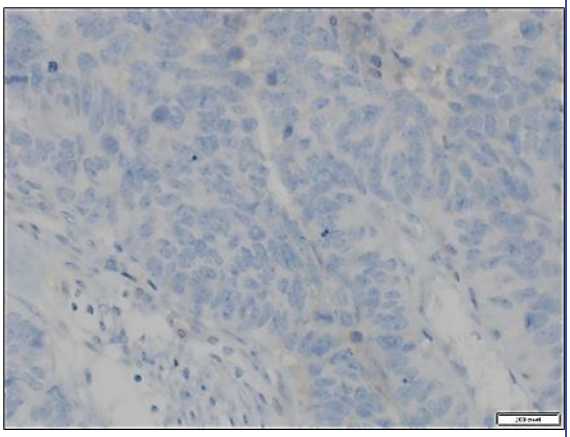
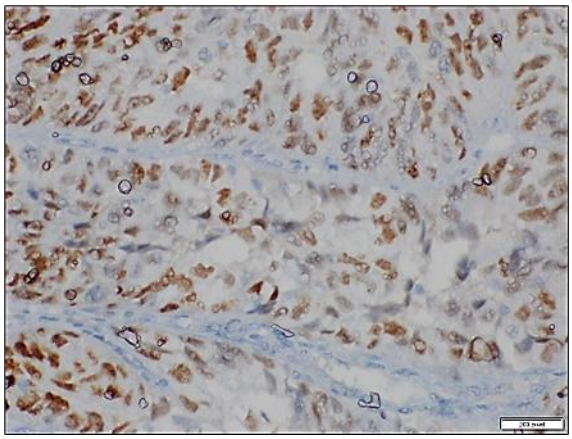
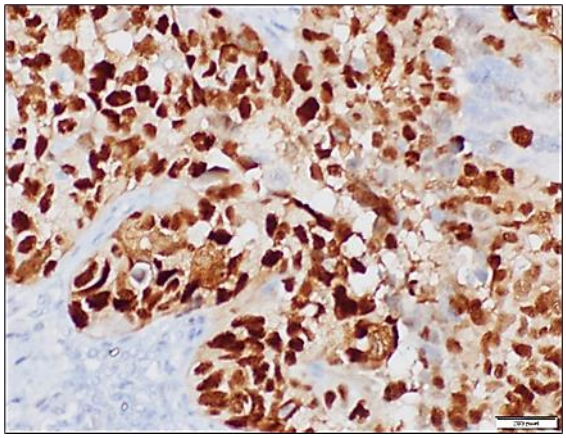
Her postoperative period was complicated by a transient viral fever, but otherwise, she had an uneventful recovery. Hypoglycaemia did not recur postoperatively. We could not confirm a drop in postoperative IGF2 levels due to financial constraints. The right-sided effusion was drained, and she was referred to the oncology team for adjuvant chemotherapy.

<table>
<tr><td>  </td><td>Hematoxylin and Eosin staining showing tumor cells with columnar configuration with moderately pleomorphic nuclei, moderate eosinophilic cytoplasm, and brisk mitoses</td></tr>
<tr><td>  </td><td>  </td></tr>
<tr><td>Positive expression of Cytokeratin 7</td><td>Negative expression of Cytokeratin 8</td></tr>
<tr><td>  </td><td>  </td></tr>
<tr><td>Positive expression of Estrogen receptors</td><td>Positive expression of Progestogen receptors</td></tr>
<tr><td colspan="2">Figure 2: Histological sections of the tumor</td></tr>
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The histology of the ovarian mass revealed fused atypical glands, papillae and solid nodules. The tumor cells exhibited a relatively columnar configuration with moderately pleomorphic nuclei, eosinophilic cytoplasm, and brisk mitoses. The stroma was desmoplastic and multiple vascular tumor emboli, capsular invasion and local infiltration of the myometrium were also observed. Findings of proliferative phase endometrium and mild chronic cervicitis were noted. Tumor metastasis was observed in the omental tissues. Immunohistochemistry showed strong expression of Cytokeratin 7 (CK7), Estrogen Receptor (ER), and Progestogen Receptor (PR) and negative expression of Cytokeratin 20 (CK20) in the tumor cells (Figure 2). These findings were consistent with a stage III C (pT3cNxMx), high-grade, endometrioid carcinoma according to the Federation of Gynecology and Obstetrics (FIGO) classification [2].

Discussion

The diagnosis of paraneoplastic hypoglycaemia is challenging due to its uncommon nature. In this particular case, the patient's initial presentation involved life-threatening coma and seizures, preceded by prodromal manifestations indicative of neuroglycopaenia and autonomic dysfunction during periods of fast. These symptoms prompted further investigation. The diagnosis of hypoglycaemia was confirmed through the observation of Whipple's triad (clinical features of hypoglycaemia, low plasma glucose levels and resolution of symptoms after correction of hypoglycaemia). Notably, the patient's symptoms primarily occurred during fasting, effectively ruling out causes of postprandial (reactive) hypoglycaemia.

Non-islet cell tumor hypoglycaemia (NICTH) which is the hypoglycaemia resulting from tumoral secretion of incompletely processed IGF2 (also known as big IGF2 or pro IGF2) was first reported in 1929 [3]. NICTH occurs with thoracic, retroperitoneal and pelvic tumors of epithelial or mesenchymal origin in about 80% of the cases, with tumors of neuroendocrine or haematopoeitic origin accounting for 1% of cases, while the primary tumor is unknown in 14% of cases [4]. The estimated incidence of NICTH is 1 case per million population, with approximately half of the cases of NICTH presenting with hypoglycaemia as the first manifestation [5]. While the liver is the primary source of IGF2 in postnatal life, the exact functions of IGF2 remain unknown. The secretion of IGF2 is not influenced by growth hormone. Although structurally similar to insulin, IGF2 has less than 5% of insulin’s hypoglycaemic potency. Thus, only supra-physiological concentrations (nearly 1000 times the normal levels) of IGF2 can potentially lead to hypoglycaemia, through various mechanisms including inhibition of hepatic gluconeogenesis, glycogenolysis, ketogenesis, lipolysis, low growth hormone secretion, reduced IGF1 activation, reduced IGF1-mediated glucagon secretion and stimulation of glucose uptake by muscles [3].

A raised or normal IGF2 with elevated IGF2/IGF1 molar ratio over 3:1 is highly supportive of IGF2 mediated NICTH [3]. Low levels of insulin, c-peptide, and beta-hydroxybutyrate are also characteristic, as observed in our case. A ratio of greater than 10:1 is considered nearly diagnostic of NICTH. Additionally, elevated pro-IGF levels and raised pro IGF2/pro IGF1 molar ratio, too, are supportive, though not measured in our case. Concurrent normal morning cortisol and renal and liver functions ruled out other

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contributory causes. The insulin-like activity of IGF2 is known to contribute to hypokalaemia, as detected in our case [6]. Rarely, acromegaloid changes due to the activation of IGF receptors by IGF-2 have been described, though not noted in our patient [7].

NICTH is managed by correcting hypoglycaemia and treating the underlying tumor. The former can be managed by encouraging frequent high carbohydrate meal intake, avoiding prolonged fasting and, if necessary, with oral glucose, intravenous dextrose or glucagon depending on severity. A daily dose of 30–60mg of prednisolone or 4mg of dexamethasone has been shown to suppress IGF2 levels in a dose dependent fashion [8]. These stimulate gluconeogenesis and potentially limit the release of IGF2. Diazoxide, octreotide, supraphysiological doses of growth hormone, which are thought to suppress peripheral glucose uptake and decrease passage of IGF2 across the endothelial barrier, have been previously tried to induce hyperglycaemia [3]. Diazoxide and octreotide may not be suitable, as they primarily act on pancreatic islet cells [5].

The presence of a large, irregular, ovarian mass adherent to adjacent structures, along with histological analysis revealing a high-grade endometrioid carcinoma with vascular tumor emboli reveals the aggressive and advanced stage of the tumor in our patient. This case contributes to the existing literature by reporting the first documented case of paraneoplastic hypoglycaemia in ovarian endometrioid carcinoma. Endometrioid ovarian carcinoma represent a distinct subtype of epithelial ovarian cancers (EOC) and is associated with endometriosis and Lynch syndrome [9]. They can be distinguished from the other subtypes of EOCs through immunohistochemistry. A study of 72 ovarian tumors revealed that a high degree of IGF2 expression correlates with poorer survival outcomes [10].

Surgical excision of the tumor is the most definitive treatment of NICTH, as it results in immediate resolution of hypoglycaemia. The successful resolution of hypoglycaemic episodes following surgical intervention strongly suggests a direct association between the ovarian tumor and paraneoplastic hypoglycaemia. Intriguingly, intraoperative hypoglycaemia, possibly due to the release of preformed insulin-like growth factor 2 (IGF2), was observed in our patient. In cases of incomplete resection, local tumor infiltration and distant metastasis, long-term follow-up and additional chemo radiotherapy or selective embolization of feeder vessels are essential to address potential systemic disease, limit metastasis or recurrence and control hypoglycaemia.

This report serves as a reminder to clinicians to be vigilant and consider less common aetiologies when evaluating patients with hypoglycaemia, particularly the presence of malignancies. By increasing awareness and understanding of this rare phenomenon, we can optimize patient care and potentially improve outcomes in similar clinical scenarios. The multidisciplinary approach involving endocrinology, gynaecology, and oncology teams was crucial in achieving a comprehensive diagnosis and guiding appropriate treatment strategies.

Conclusions

This case highlights the rare association between paraneoplastic hypoglycaemia and high-grade, malignant, ovarian endometrioid carcinoma. The unusual presentation of hypoglycaemia in this context, emphasizes the importance of considering paraneoplastic causes in patients with unexplained recurrent hypoglycaemic episodes. Surgical intervention, along with comprehensive management of the underlying malignancy, remains the cornerstone of treatment. Further research and clinical studies are warranted to better understand the pathophysiology, optimal management strategies and long-term outcomes of paraneoplastic hypoglycemia associated with ovarian malignancies.

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