

# Ectopic insulin-secretion by a large cell neuroendocrine carcinoma of the cervix

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*Key Clinical Message:* In patients presenting with hyperinsulinaemic hypoglycaemia with a non-pancreatic neuroendocrine tumour, the diagnosis of an ectopic insulin-secreting tumour should be considered, and investigated further with confirmatory insulin staining.

*Case presentation:* Endogenous hyperinsulinaemic hypoglycaemia is most commonly attributed to pancreatic islet-cell tumours. We present a case of an insulin-secreting cervical neuroendocrine carcinoma causing significant hypoglycaemia.

A 62 year-old postmenopausal female presented with postcoital bleeding, on a background of two normal vaginal childbirths, tubal ligation and menopause at age 42. She had no other significant medical history, was a lifelong non-smoker, did not drink alcohol, and took no prescribed medications. Vaginal speculum examination, followed by hysteroscopy, demonstrated a tumour of the cervical lip. Papanicolaou smear and biopsy confirmed a human papilloma virus-18 positive cervical cancer. There were intermediate size, malignant cells with oval, hyperchromatic and overlapping nuclei, frequent mitosis, and necrosis. Tumour cells stained positively for p16, CD56 and synaptophysin, consistent with a neuroendocrine tumour.

Ultrasound, computed tomography (CT) and FDG-positron emission tomography (PET) confirmed a 3x4cm cervical mass without nodal or distant metastases, and a diagnosis of Stage IB2 neuroendocrine carcinoma of the cervix was made. She completed six cycles of carboplatin and etoposide with curative intent, followed by external beam radiotherapy and brachytherapy with a total biological equivalent dose of 90.8 Gy. A restaging FDG-PET scan prior to completion of chemotherapy showed incomplete metabolic response in the cervix, but no local nodal or metastatic disease. Post-treatment biopsy demonstrated a tumour comprised of intermediated size neoplastic cells arranged in a nested pattern [Figure 1a]. The tumour cells demonstrated neuroendocrine differentiation and a Ki-67 proliferation index of 30%.

At 12 months post-diagnosis, the patient presented to the emergency department with an episode of symptomatic hypoglycaemia (plasma glucose 1.7mmol/L) occurring in the fasted state. She was not receiving any antidiabetic treatment. She exhibited sinus tachycardia to 120bpm, sweating and tremor. Symptoms were promptly corrected by administration of glucose, fulfilling Whipple's triad. The patient also demonstrated marked pitting oedema of the lower limbs without evidence of cardiac failure. Biochemical studies demonstrated normal renal function (estimated glomerular filtration rate >90) and electrolytes, but marked liver function derangement, hypoalbuminaemia to 21g/L [normal range 35-50], normocytic anaemia to 75g/L [normal range 115-165] and thrombocytopenia to  $25 \times 10^9$ /L [normal range 150-400]. During one episode of recurrent hypoglycaemia, when plasma glucose was 2.2mmol/L, serum c-peptide was 2.33nmol/L [normal range 0.26-1.73] and serum insulin 19mIU/L [normal range <9]. Chest x-ray revealed widespread cannonball pulmonary metastases [Figure 2] and computed tomography revealed hepatic metastases, persistence of the cervical mass, and no evidence of a pancreatic lesion. Retrospective review of the cervical biopsy with further

immunohistochemistry revealed positive staining for insulin and negative staining for glucagon confirming that her symptoms were due to an insulin-secreting neuroendocrine carcinoma (NEC) [Figure 1b].

Initial treatment with intravenous boluses of 50% dextrose, maintenance 10% dextrose and intravenous hydrocortisone 100mg QID were insufficient to maintain normoglycaemia. Based on suspicions of an insulin-secreting neuroendocrine carcinoma, the subcutaneous somatostatin analogue octreotide was commenced at 200mcg q8hrly. This allowed the cessation of intravenous dextrose and hydrocortisone and clinically significant improvement in hypoglycaemia. Acute hypoglycaemic events were managed with oral glucose and PRN subcutaneous glucagon 1mg. In view of progressing aggressive malignancy and poor performance status a palliative approach to management was decided. The patient died on day 20 of admission.

Neuroendocrine neoplasms (NENs) are malignancies that arise from neuroendocrine cells and may have the ability to produce and secrete peptide hormones. They typically originate in lung, gastro-intestinal tract or pancreas. NENs of the uterine cervix are rare and account for 0.9-1.5% of all cervical cancers<sup>1</sup>. Recent updates to the classification of NEN, which emphasise tumour grade as opposed to anatomical origin, distinguish low-grade neuroendocrine tumours from high-grade NECs<sup>2</sup>. Large cell NECs, as in this case, are less common than small cell NECs and are characterised morphologically by cells which are organised in organoid or trabecular patterns, with abundant cytoplasm, large nuclei with prominent nucleoli and high mitotic rate. Large cell NECs usually have relatively lower Ki-67 proliferation index compared to small cell NECs which always demonstrate >90% proliferation index. Diagnosis is confirmed by positive immunohistochemistry for neuroendocrine markers (synaptophysin, CD56 and chromogranin).

Staging is determined by the International Federation of Gynecology and Obstetrics (FIGO) system<sup>3</sup>. Our patient at time of diagnosis had a 3x4cm primary lesion of the uterine cervix without nodal or distant metastases detected by PET. In conjunction with tissue morphology and immunohistochemistry, this supports a diagnosis of a Stage 1B2 large-cell neuroendocrine carcinoma of the cervix.

Due to the rarity of cervical NECs, no randomised controlled trials have been undertaken to guide management. Instead treatment is informed by retrospective studies and treatment approaches extrapolated from the treatment of NEN arising from other organs such as small cell lung cancers. Typically a multi-modal approach is utilised involving radical surgery, radiotherapy and chemotherapy involving etoposide and either carboplatin or cisplatin. Despite therapy, prognosis for cervical NECs remain poor, with a 5 year survival of 36%<sup>4</sup>.

Non-islet cell tumours secreting insulin are infrequently reported, and comprise 1-2% of insulinomas<sup>5</sup>, most commonly arising in peripancreatic or periduodenal regions. Ectopic insulin-secretion has been reported in pheochromocytomas, and NENs of the kidney, liver, ovary, lung and cervix<sup>5</sup>. Positive insulin immunohistochemistry in the tumour, in combination with elevated c-peptide and insulin levels suggests that the insulin-secreting tumour was the aetiology for the patient's hypoglycaemia. Interestingly, there had been no previous history of symptomatic hypoglycaemia in the year since diagnosis and it is likely that declining hepatic gluconeogenesis due to an increasing metastatic tumour burden was a contributing factor in the pathophysiology. We are aware of only two previously reported cases<sup>6-7</sup> of insulin-induced hypoglycaemia originating from a cervical NEN, one of which was small-cell, and the other a squamous cell carcinoma, although notably large-cell NECs were frequently under-recognised and misdiagnosed as squamous cell carcinomas at the time of its report<sup>7</sup>. In one patient, octreotide offered minimal clinical improvement and she required diazoxide and intravenous glucose<sup>6</sup>. While resection of insulinoma is treatment of choice, medical therapy is considered for unresectable metastatic disease or poor surgical candidates. Diazoxide inhibits  $\beta$ -cell insulin release and enhances glycogenolysis, however was not used in our patient due to her generalised oedema and the propensity for diazoxide to cause fluid retention<sup>9</sup>. Octreotide binds to somatostatin receptor type 2 and inhibits insulin, among other hormones<sup>9</sup>. Phenytoin and verapamil also inhibit insulin release and have been used with varied success<sup>9</sup>. Endoscopic ultrasound-guided ethanol ablation and CT-guided radiofrequency ablation of pancreatic insulinomas are minimally invasive procedures also considered in poor surgical candidates<sup>10-11</sup>.

Ectopic insulin-secreting neuroendocrine tumours are exceedingly rare, but should be considered as a differential diagnosis for hyperinsulinaemic hypoglycaemia.

#### *Data Availability Statement:*

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

#### *Author Contributions:*

MW was involved in the management of the case and wrote the manuscript.

QV assisted in the writing of the manuscript.

WV was involved in the immunohistochemistry of the specimen and assisted in the writing of the manuscript.

MM was involved in the management of the case, and editing of the manuscript.

#### *Conflict of Interest Statement:*

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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#### *List of Legend Figures:*

Figure 1a: Haematoxylin & Eosin stained section showing the large cell morphology and nested arrangement of cells (x400)

Figure 1b: Tumour cells display positive staining for Insulin (x200)

Figure 2: Multiple bilateral pulmonary nodules in keeping with metastases, increased bilateral interstitial opacities, small right pleural effusion with mild right lower zone atelectasis.



