

# Triple-negative breast cancer with ACTH-dependent Cushing's syndrome – case report

## Authors' Contribution:

A – Study Design  
B – Data Collection  
C – Statistical Analysis  
D – Data Interpretation  
E – Manuscript Preparation  
F – Literature Search  
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## ABSTRACT:

**Introduction:** Endocrine and metabolic paraneoplastic syndromes in the course of malignant tumours result from ectopic production of hormones or hormone precursors in tumour cells. Production of hormones by endocrine tumours is relatively frequent, while such a production by adenocarcinoma cells is definitely rare. The study presents a case of a triple-negative invasive breast cancer, with ectopic secretion of ACTH (adrenocorticotrophic hormone), which provokes serious metabolic disorders.

**Materials and methods:** The patient was admitted to hospital with symptoms of Cushing's syndrome. Diagnostic tests revealed that the cause of metabolic disorders was breast cancer. After proper preparation, the patient was qualified for surgery.

**Results:** After mastectomy the patient's metabolism stabilised. The patient underwent adjuvant chemotherapy and radiotherapy. Four months after the last cycle of systemic treatment, cancer dissemination was found. The patient was treated with second-line chemotherapy, however control CT revealed progression. The patient died 20 months after surgery and two months after the last cycle of chemotherapy.

**Conclusions:** The case reported in this study – triple-negative invasive breast cancer, responsible for ectopic production of ACTH and causing Cushing's syndrome – is a rare phenomenon. Treatment of patients with breast cancer showing hormonal activity should not differ from general rules applied for breast cancer. However, due to accompanying metabolic disturbances, the patients need individualised oncological approach, precise diagnostic tests and adequate preoperative preparation.

## KEYWORDS:

breast cancer, paraneoplastic syndrome, ACTH, adrenocorticotropin, Cushing's syndrome

## INTRODUCTION

Endocrine and metabolic paraneoplastic syndromes, occurring in 5–10% of malignant tumours, result from ectopic production of hormones or hormone precursors in tumour cells. One of the most frequently produced hormones is adrenocorticotropin, which is responsible for increased cortisol secretion from adrenal cortex and occurrence of Cushing's syndrome symptoms. Patients usually develop hypertension, diabetes mellitus, osteoporosis and alkalosis with low plasma potassium level. Other possible symptoms include: characteristic distribution of fat tissue (central obesity and the so called «buffalo hump»), muscle weakness, stretch marks on the skin, acne, emotional lability, and – in women – disturbed menstrual cycle. The documented sources of ectopic ACTH, produced by nonpituitary cancers, include some small cell lung cancers, pancreatic islet cell tumours, thymomas, medullary thyroid cancers, bronchial carcinoid tumours, and hepatic carcinoid tumours [1–4]. Production of adrenocorticotropin by glandular cancers [1–5], especially breast cancer, is sporadic (<1%) [6–8]. The study presents a case of a triple-negative invasive breast cancer with neuroendocrine differentiation and ectopic production of ACTH.

## CASE REPORT

A 57-year-old woman with recently diagnosed diabetes mellitus type 2, grade 3 hypertension according to ESC (European Society of Cardiology), central obesity and no family history of cancer, was admitted for diagnostic tests of hypercorticism occurring with severe hypokalemia (1.6 mmol/L) and cardiac insufficiency. The patient also had muscle weakness and stretch marks on the skin.

During hospitalisation, biochemical tests confirmed the working diagnosis, ACTH-dependent Cushing's syndrome (cortisol level at 6 a.m. 125.1 µg/mL [5–25 µg/dL]; cortisol level at 12 pm 73.70 µg/dL [0–5 µg/dL]; 17-OHCS level in 24-hour urine collection 30.2 mg/24h [2.2–7.0 mg/24 h]; ACTH level 280 pg/mL [6.0–56.0 pg/mL]; Aldosterone level 33.70 pg/mL [7.5–60 pg/mL]). The bone density scan, magnetic resonance imaging of the head, computed tomography of the abdomen and chest, as well as scintigraphy were performed to differentiate the cause of Cushing's syndrome between ectopic ACTH secretion, hormonally active adrenal tumor and hormonally active pituitary tumor (Cushing's disease). A bone density scan showed slightly lowered bone density. Imaging examinations showed bilateral adrenal hyperplasia, no focal lesions in the pituitary gland, and a stage cT3N1M0 cancer lesion in the superior lateral quadrant of the right breast. A scintigraphy with 99m-Tc-labelled somatostatin analogue showed increased receptor expression in the described breast tumour (Fig. 1). In both mammogram and US examination, the tumour was well defined and it had polycyclic outline. A histopathological examination of a biopsy specimen revealed an infiltration of cancer with a triple-negative receptor status (estrogen receptor – 0; progesterone receptor – 0; HER2 [human epidermal growth factor receptor 2] – 2+; FISH [fluorescent in situ hybridization] – negative; Ki67 > 50%). An immunohistochemical test confirmed it was an epithelial tumour (positive reaction for the presence of cytokeratins AE1 and E3 and epithelial membrane antigen [EMA]). Following oncological and surgical consultation, due to increased metabolic disturbances, the idea of induction chemotherapy was abandoned, and the patient was qualified for surgical treatment. At the preoperative stage the patient received steroidogenesis inhibitors (mitotane and metyrapone) and somatostatin analogue (octreotide), her diabe-

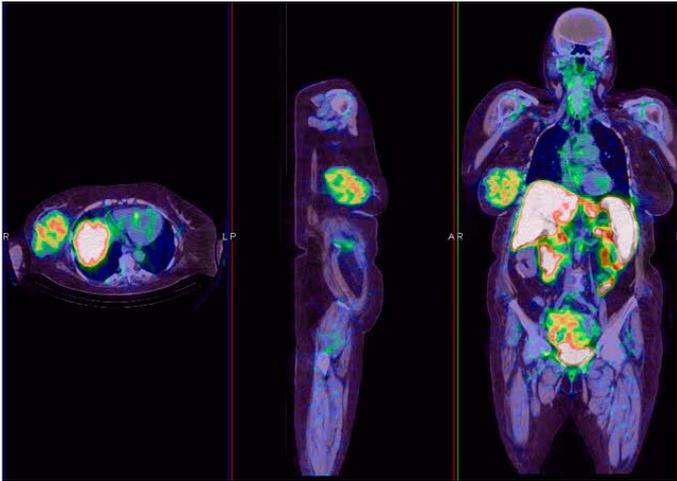


Fig. 1. SPECT/CT scan after administration of  $^{99m}\text{Tc}$ -somatostatin analogue showing the presence of somatostatin receptors in the right breast tumor.

tes was controlled with insulin therapy and kalemia was stabilised at 3.0 mmol/L. Due to symptoms of cardiac insufficiency and diagnosed thrombocytopenia (51000/ $\mu\text{l}$  with normal bone marrow biopsy results) the patient also required preoperative cardiac and haematological preparation. During the patient's stay at the surgery ward, a modified radical mastectomy of the right breast was performed using the Madden technique. There were no postoperative complications. Within the subsequent 14 days of hospitalisation, the patient's metabolism gradually stabilised, the level of ACTH and cortisol in blood serum normalised (cortisol 16.86  $\mu\text{g/dL}$  [8 am], ACTH 9.8 pg/mL) and the number of platelets became stable. The patient was then discharged from the hospital. Histopathological examination of a surgical specimen allowed to diagnose invasive breast cancer with neuroendocrine differentiation G3 at stage pT3N1a. In 3 out of 23 excised lymph nodes, macrometastases were found, the largest with a diameter of 19 mm, extending from the lymph node capsule and infiltrating the surrounding fat tissue. Isolated cancer cells were found in further two lymph nodes. Immunohistochemically, the cancer cells indicated the presence of NSE (neuron-specific enolase) in less than 50% of cells. However, expression of chromogranin, synaptophysin, CD56, TTF1, CK5/6, p63 and somatostatin receptors (carried out using rabbit antibodies SSTR 1-5 (Gramsch Laboratories) at a dilution of 1/500) was not found. The triple-negative nature of the cancer (ER-0, PGR-0, HER2-negative) was confirmed. At the next stage, the patient received adjuvant treatment in another clinic, closer to her place of residence. Probably based on the neuroendocrine character of the tumor, she was qualified for adjuvant EP chemotherapy (VI cycles of etoposide and cisplatin). The patient was treated also with radiotherapy. Four months after the last cycle, metastases to the liver and mediastinal lymph nodes were found in CT. In scintigraphy with  $^{99m}\text{Tc}$ -labelled somatostatin analogs, metastases showed no expression of the receptor. The patient underwent second-line chemotherapy, but control CT revealed progression of liver metastases and bone dissemination. Finally, the patient died 20 months after surgery and two months after the last cycle of chemotherapy.

## DISCUSSION

The term paraneoplastic syndrome is used to describe a group of symptoms occurring in the course of cancer and resulting not

from the presence of the tumour or metastasis, but from endocrine activity of the tumour. Ectopic production occurs the most frequently with respect to the following hormones: adrenocorticotropic, human chorionic gonadotropin (HCG), antidiuretic hormone (ADH), parathormone (PTH), growth hormone (GH), prolactin (PRL), gastrin, glucagon, renin and erythropoietin. These substances produced by tumour cells may cause metabolic, dystrophic and/or degenerative changes of various degrees of intensity.

In literature, neuroendocrine differentiation of primary breast cancer occurs in approximately 21% of cases [9]. It is estimated that in 16% of patients, especially after menopause, expression of ACTH can be found [6]. Contrary to bronchial carcinoid tumours and small cell lung cancers causing ectopic production of adrenocorticotropic, where a majority of patients have clinically overt hypercorticism [1–3], breast cancers with hormonal activity give Cushing's syndrome symptoms only in 1% of cases [7]. This fact can be explained by slight, subclinical production of hormones, which can be detected in biochemical tests, but insufficient to cause clinical symptoms. Immunohistochemical profile found in the histopathological examination did not allow to diagnose primary neuroendocrine cancer, but only cancer with neuroendocrine differentiation. From the clinical perspective, increased metabolic disturbances proved very important – they made it difficult to prepare the patient and provide care during the perioperative period, which was also indicated in other papers [8, 10]. Hormonal and metabolic status of the patient stabilised over a short time after the radical surgery, which was reported by other authors [10].

Contrary to other reports, we found an atypical, triple-negative nature of the tumour. Previously described 6 cases of breast cancer producing adrenocorticotropic always had high expression of hormonal receptors, especially the estrogen receptor [4, 8]. Explanations given to this phenomenon indicated the participation of ACTH in carcinogenesis dependent on steroid hormones. Ectopic production of ACTH caused by a triple-negative cancer denies such a relationship and indicates the necessity to seek other theories.

Prognosis in primary breast cancers with ACTH production depends on tumour biology and cancer staging; it is clearly better in cases with low, clinically insignificant concentrations of adrenocorticotropic [9]. High concentration of hormones, advanced stage of tumour, high histological grade and triple-negative molecular subtype in the described case, were adverse prognostic factors and indicated a necessity of aggressive adjuvant treatment.

In the presented case, the etoposide and cisplatin chemotherapy reserved for neuroendocrine tumors is highly controversial. In the opinion of the authors, anthracyclines in combination with taxanes would be more reasonable, however, due to the change of the treatment center it is difficult to undertake appropriate discussion.

## CONCLUSIONS

Although there are no definitive guidelines for the treatment of this type of cancer, it appears that the strategy should not deviate from the general rules of breast cancer treatment. Coexistence of serious hormonal and metabolic disturbances – like in the presented case – indicates that it is necessary to use an individualised approach in the oncological treatment.

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