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Ectopic ACTH syndrome caused by thymic neuroendocrine tumour — stages of treatment

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Thymic neuroendocrine tumours (NETs) are a rare group of neoplasms classified according to morphological criteria as typical and atypical (well-differentiated) carcinoids, and large-cell neuroendocrine carcinomas and small-cell carcinomas (poorly differentiated) [1]. Atypical thymic carcinoids are characterised by high malignancy, short survival, frequent recurrence and metastasis. They can be hormonally active and then they most commonly manifest as Cushing syndrome (CS) secondary to ectopic adrenocorticotropic hormone (ACTH) production [2]. This article describes a severe course of atypical thymic carcinoid with ectopic ACTH secretion.

A 32-year-old female patient with hypertension, decompensated diabetes mellitus, severe hypokalaemia and phenotypic features of CS was admitted to the Department of Endocrinology in May 2021. Based on the endocrine diagnosis — lack of cortisol suppression after low and high dose dexamethasone (23.1 ug/dL; 29.2 ug/dL, respectively) with persistently high ACTH levels and normal pituitary magnetic resonance imaging, ectopic CS was diagnosed. During the search for the source of ACTH secretion, a computed tomography (CT) scan of the chest was performed, which showed a pathological mass in the mediastinum. The tumour, measuring 42 × 43 × 40 mm, was compressing the superior vena cava, causing critical narrowing of its lumen and involving the initial segment of the brachiocephalic trunk; in addition, several foci of a similar nature were observed to the left of the pathological mass. Therapy with the adrenal steroidogenesis inhibitor — metyrapone at gradually increasing doses was commenced. An endobronchial ultrasound-guided transbronchial needle aspiration of the mediastinal tumour was performed. In histopathology, atypical carcinoid with a proliferation index (Ki-67) of 10% was diagnosed. A long-acting somatostatin analogue, lanreotide at 120 mg every 28 days, was implemented and treatment with metyrapone was continued. [^{68}Ga]Ga-DOTA-TATE confirmed a tumour-like lesion in the anterior mediastinum with pathologically increased radiolabel accumulation [maximum standardised uptake value (SUVmax) 19.75] (Fig. 1A). Definitive radiotherapy to the mediastinal tumour area and mediastinal lymph nodes was conducted between 25/10/2021 and 12/12/2021 at a total dose of 66 Gy after which anatomical examination showed a reduction in the main tumour mass and improved hormonal control of the disease (Tab. 1). This enabled a median sternotomy with radical resection of the anterior mediastinal tumour to be conducted on 24/06/2022 with resection of the left and right brachiocephalic vein, the superior vena cava and a fragment of the right phrenic nerve with implantation of Gore-tex prosthesis with rings between the right brachiocephalic vein and the superior vena cava complicated by respiratory failure and cardiac tamponade. The resected tumour was assessed pathomorphologically and diagnosed as atypical thymic carcinoid with infiltration of the superior vena cava with metastasis to the thoracic lymph nodes (pT3N1, R1, Ki-67 20%, mitotic rate 2/2 mm^2). After surgery, a significant reduction in CS symptoms, normalisation of blood pressure and resolution of diabetes was achieved. A remission of hypercortisolaemia was confirmed by hormonal testing, which enabled the discontinuation of treatment with metyrapone (Tab. 1). Biochemical remission lasted 11 months. Increased radiolabel expression in bone lesions was shown for the first time in imaging with [^{68}Ga]Ga-DOTA-TATE performed on 13/12/2022 (Fig. 1C). In May 2023, there was a recurrence of full-blown hypercortisolemia

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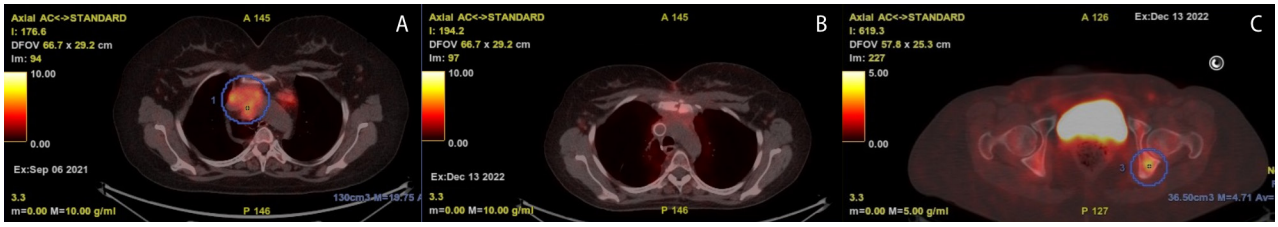

Figure 1. *[^{68}Ga]Ga-DOTA-TATE PET/CT scans.* **A.** *Tumour-like lesion in the anterior superior mediastinum;* **B.** *Postoperative condition, no visible change in the anterior mediastinum;* **C.** *Increased somatostatin receptor expression in the left ischium in the area of the left hip joint acetabulum*

Table 1. Patient's laboratory results — initial and during follow-up

Parameters	August 2021	February 2022 a month after radiotherapy	October 2022 three months after surgical treatment	July 2023 CS symptoms recurrence	December 2023	May 2024 further disease progression
ACTH [pg/mL] (ref. range 7.20–63.3)	284.40	267.40	54.74	228.40	287.30	468.40
Cortisol 8 am [μg/dL] (ref. range 4.82–19.50)	35.40	15.35	11.90	39.37	28.55	22.79
Cortisol midnight [μg/dL]	35.88	7.46	0.72	39.79	18.26	19.94
24 h urine free cortisol [μg/dL] (ref. range varies)	3088.05 [36.00–137.00]	68.40 [36.00–137.00]	12.76 [4.30–176.00]	2201.00 [11.00–70.00]	965.00 [11.00–70.00]	473.00 [11.00–70.00]
Late night salivary cortisol [μg/dL] (ref. range < 0.41)	NA	NA	NA	5.35	2.59	1.65
Cortisol 1 mg DST [μg/dL]	NA	NA	0.63	39.39	NA	NA

ACTH — adrenocorticotropic hormone; CS — Cushing syndrome; DST — dexamethasone; NA — not available

confirmed by hormonal tests (Tab. 1). From 26/07/2023, osilodrostat was included in the treatment at a gradually increasing dose. Subsequent CT scans showed foci of active tumour infiltration in the mediastinum and multiple metastatic sclerotic foci in the skeletal system. From 15/07/2024, chemotherapy according to the capecitabine and temozolomide regimen was commenced. Unfortunately, bone marrow aplasia occurred during the first cycle of temozolomide treatment, which ultimately led to the patient's death.

The available literature demonstrates that surgical resection is crucial for the length of survival of patients with thymic NET and should be pursued whenever possible [3]. In the case described here, preoperative radiotherapy was used followed by aggressive surgical treatment; in addition, hypercortisolaemia was properly managed and the antiproliferative effect of lanreotide was utilised [4]. However, the use of multimodal treatment of a locally advanced disease may not provide benefits in terms of survival [3]. Advanced clinical stage, tumour size and incomplete resection are the main causes of high mortality. It is important to note that there are still no clear guidelines regarding the role of chemotherapy in the treatment of thymic NET [4, 5]. Its use during progression in patients with multiple CS complications can lead to life-threatening complications as illustrated by the case presented.

Author contributions

Both authors contributed to the conception, design, and drafting of this submission in its final format.

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Conflict of interest

Authors declare no conflict of interests.

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