Submitted: 28.11.2021
Accepted: 06.12.2021
Early publication date: 25.03.2022

Endokrynologia Polska
DOI: 10.5603/EP.a2022.0015
ISSN 0423–104X, e-ISSN 2299–8306
Volume/Tom 73; Number/Numer 2/2022

Therapeutic difficulties in an aggressive ACTH-secreting pituitary adenoma

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Key words: *aggressive ACTH-secreting pituitary tumour; treatment; temozolomide*

Aggressive pituitary adenomas are rare diseases, and their treatment is a major challenge for clinicians. High-potential aggressive pituitary tumours include non-functioning corticotroph adenomas (silent corticotroph adenomas), which can transform, even many years after diagnosis, into invasive ACTH-secreting tumours resistant to standard therapies, including surgery, radiotherapy, and established medical therapy (e.g. pasireotide and cabergoline) [1]. The presented case involves a 39-year-old man with a diagnosed non-functioning pituitary macroadenoma sized 39 × 38 × 40 mm, compressing the optic chiasm and infiltrating the right cavernous sinus on pituitary magnetic resonance imaging (MRI), performed in July 2013 due to right temporal hemianopia. In August 2013 a non-radical transsphenoidal resection of the pituitary tumour was performed [histopathology: acidophil pituitary adenoma, focal positive for adrenocorticotropic hormone (ACTH), growth hormone (GH), prolactin (PRL), and luteinizing hormone (LH) and negative for thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), LH; p53, Ki67 weakly positive], with radical vision improvement. Due to the hypopituitarism with secondary hypothyroidism, hypogonadism, and diabetes insipidus, substitutive therapy with levothyroxine, testosterone, and desmopressin was started and continued until now. ACTH, cortisol, GH, and insulin-like growth factor (IGF) levels were in normal range, and the PRL level was low (Tab. 1). The postoperative pituitary MRI (December 2013) showed a large residual tumour mass (32 × 32 × 31 mm), without compression of the optic chiasm, and therefore a stereotactic radiotherapy (CyberKnife) was performed (August 2014), leading to regression of the adenoma, persisting until 2017. A subsequent MRI scan (July 2017) showed increased tumour volume within the sella turcica and pathological remodelling of the clivus. Due to the suspected independent neoplastic lesion, an endoscopic transsphenoidal biopsy of the clivus tumour was performed in September 2017 (histopathology: a spongy bone with numerous diffuse foci of necrosis, with clusters of small acidophilic cells originating from the pituitary gland, ACTH (+), Ki67 5%). Plasma ACTH and serum cortisol levels were within reference values (Tab. 1). A diagnosis of silent corticotroph adenoma was made, and radiotherapy with 6 MV X photons to the area of adenoma recurrence (df 7 Gy to dc 21 Gy) was administered, resulting in stabilisation of the tumour size. Re-progression of the adenoma was demonstrated in the pituitary MRI in December 2019 in the form of a massive tissue infiltration crossing all bone constraints of the sella turcica, penetrating towards the right orbit (with atrophic neuropathy of the right optic nerve) and towards the skull base. At that time, diplopia and symptoms of Cushing's syndrome appeared. Hormonal tests confirmed ACTH-dependent hypercortisolaemia, and CRH test suggested an ectopic ACTH secretion (Tab. 1). Based on structural (CT of the thorax, abdomen and pelvis) and functional (^{18}F-FDG PET CT and ^{68}Ga-DOTA-TATE PET CT) imaging studies, the presence of foci of extrapituitary ACTH secretion was excluded. It was assumed that a silent corticotroph adenoma was transformed into an aggressive pituitary ACTH-secreting tumour. Following several neurosurgical consultations, the transsphenoidal partial removal of the sella turcica tumour was performed in November 2020 [histopathology: corticotrophic pituitary adenoma, ACTH (+), GH (–), PRL (–), TSH (–), FSH (–), LH (–), alpha subunit (–),

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Table 1. *Results of the patient's hormonal tests assessing the hypothalamic-pituitary-adrenal axis*

	2013–2018	December 2019	September 2020	January 2021 Before pasireotide and cabergoline treatment	June 2021 After 6 cycles of pasireotide and cabergoline treatment	October 2021 After 3 cycles of temozolomide treatment
Plasma ACTH [n. 7.2–63.3 pg/mL]	55.02–60.6	154.30	331.10	290.40	405.40	139.50
Serum cortisol 8.00 [n. 5.00–25 ug/mL]	6.63–12.6	34.35	26.33	21.54	63.29	11.65
Serum cortisol 18.00 [ug/mL]	5.18–8.4	28.72	23.70			
Serum cortisol 23.00 [ug/mL]	2.03–2.9	25.17	29.10	29.20	48.96	8.63
Urine free cortisol [n. 36–137 ug/24 h]		39.90 28.16	32.88	716.20	1075.50 5633.50	23.54 23.37
Serum cortisol in Dexamethasone test — 1 mg [ug/mL]		33.07	29.90			6.03
Serum cortisol in Dexamethasone test — 8 mg [ug/mL]			18.75			
Plasma ACTH in CRH test [pg/mL]		0'–183.00 15'–203.80 30'–175.20 60'–179.20		0'–281.00 15'–269.50 30'–267.70 60'–248.20		

Ki67 5%], obtaining a slight reduction in tumour size in MRI (January 2021). To control ACTH-dependent hypercortisolaemia, pasireotide and cabergoline therapy was administered without clinical and hormonal improvement. In an MRI scan (June 2021), the pituitary tumour was stable (Supplementary File — Fig. S1). Due to severe symptoms of hypercortisolaemia, steroidogenesis inhibitors or bilateral adrenalectomy were considered, taking into account the risk of corticotroph tumour growth. At the same time, according to European Society of Endocrinology recommendations [2], chemotherapy with temozolomide (TMZ) was started. Temozolomide is an alkylating chemotherapeutic drug approved for the treatment of glioblastomas, which damages DNA in the process of methylation, resulting in cell death. During the administration of the drug at a dose of 300 mg/day *p.o.* for 5 days, in cycles repeated every 28 days, a spectacular clinical improvement was observed (withdrawal of diplopia and symptoms of cardiac insufficiency, improvement in pharmacological control of hypertension and diabetes, enabling the discontinuation of insulin therapy, improvement of physical condition) without side effects. Hormonal tests performed after 3 cycles of chemotherapy with TMZ showed a significant decrease in plasma ACTH levels, normalization of serum cortisol levels, and reduction of the urine free cortisol to a value below the normal range (Tab. 1). A follow-up pituitary MR scan (8.10.2021) showed a slight reduction in tumour size (Supplementary File — Fig. S2). These results confirm the efficacy of temozolomide in controlling hypercortisolaemia in patients with aggressive ACTH-secreting adenomas reported in the literature [3, 4]. The early good response to TZM treatment in the presented case is promising. Continuation of temozolomide therapy was recommended, although the long-term effects of this treatment are uncertain.

CLINICAL VIGNETTE

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