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Long-term complete remission of Crooke's corticotropinoma after temozolomide treatment

Długotrwała całkowita remisja guza kortykotropowego z komórek Crooke'a po leczeniu temozolomidem

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Abstract

Introduction: Crooke's corticotropinomas are the unique cause of Cushing's disease. The majority of them are aggressive macroadenomas, refractory to conventional therapy, with a high recurrence rate. The aim of the study was the presentation, in relation to data from the literature, of a case of a patient with ACTH-dependent Cushing's syndrome caused by recurrent Crooke's cells corticotropinoma, who achieved 33-month complete remission after treatment with temozolomide (TMZ).

Case report: A 54-year-old man was diagnosed with Cushing's disease five years earlier on the basis of a typical clinical picture and hormonal tests. MRI revealed 32 × 29 × 24 mm macroadenoma. The patient underwent three subtotal selective transsphenoidal adenomectomies without retirement of hypercortisolaemia. A postoperative pathologic exploration revealed a densely granulated corticotroph Crooke's cells adenoma with MIB-1 index < 1%. Because of the large size of the tumour with its expansion to both cavernous sinuses and suprasellar region together with a compression of the optic chiasm, the patient was disqualified for gamma–knife. Due to an exhaustion of all conventional therapeutic options the patient was qualified to TMZ therapy. The standard dose of TMZ (150 g/m^2) for five days every 28 days was implemented. After three courses of TMZ pronounced regression of tumour size with a marked hormonal and clinical improvement was certified. After six courses, consecutive tumour regression was observed. Nine courses resulted in a total radiological tumour shrinkage and hormonal normalisation. Despite the cassation of TMZ treatment the complete remission of the disease maintained for 33 months.

Conclusion. Temozolomide can be an effective treatment option in invasive Crooke's cell corticotropinoma. **(Endokrynol Pol 2016; 67 (5): 526–533)**

Key words: *Crooke's cell corticotropinoma; Cushing's disease; pituitary adenoma; temozolomide*

Streszczenie

Wstęp. Guzy kortykotropowe z komórek Crooke'a są rzadką przyczyną choroby Cushinga. Większość z nich stanowią agresywne makrogruczolaki, oporne na konwencjonalne leczenie, o wysokiej częstości nawrotów. Celem pracy była prezentacja, w odniesieniu do danych z literatury, przypadku pacjenta z ACTH-zależnym zespołem Cushinga spowodowanym nawrotowym makrogruczolakiem kortykotropowym przysadki z komórek Crooke'a, który uzyskał 33-miesięczną całkowitą remisję po terapii temozolomidem (TMZ).

Opis przypadku: Mężczyzna w wieku 54 lat z chorobą Cushinga rozpoznaną pięć lat wcześniej na podstawie typowego obrazu klinicznego i badań hormonalnych. Rezonans magnetyczny wykazał obecność gruczolaka przysadki wielkości 32 × 29 × 24 mm. Pacjent przebył trzy przezklinowe zabiegi subtotalnej selektywnej adenomektomii bez normalizacji kortyzolemii. W pooperacyjnym badaniu histopatologicznym potwierdzono obecność bogatoziarnistego gruczolaka kortykotropowego z komórek Crooke'a z MIB-1 < 1%. Ze względu na duży rozmiar guza i jego ekspansję do zatok jamistych i okolicy nadsiodłowej oraz uciskiem na skrzyżowanie nerwów wzrokowych, pacjenta zdyskwalifikowano od leczenia gamma-knife. Z uwagi na wyczerpanie wszystkich konwencjonalnych możliwości terapii, chorego zakwalifikowano do leczenia TMZ. Zastosowano typowy schemat i dawkę TMZ 150 mg/m^2 przez pięć kolejnych dni, co 28 dni. Już po 3 kursach zaobserwowano znaczącą regresję wielkości guza z wyraźną poprawą kliniczną i hormonalną. Po 6 kursach potwierdzono dalsze zmniejszenie rozmiarów gruczolaka. dziewięć kursów spowodowało całkowitą radiologiczną i hormonalną remisję choroby. Mimo zakończenia leczenia TMZ pełna remisja choroby utrzymuje się od 33 miesięcy.

Wniosek: Temozolomid może być skuteczną opcją terapeutyczną w inwazyjnych gruczolakach kortykotropowych z komórek Crooke'a. **(Endokrynol Pol 2016; 67 (5): 526–533)**

Słowa kluczowe: *guz kortykotropowy z komórek Crooke'a; choroba Cushinga; gruczolak przysadki; temozolomid*

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Introduction

Crooke's cells are corticotrophs with cytoplasmic accumulation of cytokeratin filaments. The non-neoplastic Crooke's cells are common pituitary cells in patients with Cushing's disease, ectopic Cushing's syndrome, cortisol-producing adrenal tumours, and people treated with therapeutic doses of exogenous glucocorticoids [1, 2].

Normal corticotrophs contain a small number of perinuclear cytokeratin filaments. Chronic high levels of blood cortisol lead to a reduction and displacement of cytoplasmic organelles and secretory granules, and to an accumulation of Crooke's filaments. The Crooke's hyaline changes represent a symptom of corticotroph response to glucocorticoids excess, functional blockade of ACTH production, and a disruption of the secretory process [1, 2].

So far it has not been clearly explained why neoplastic Crooke's cells produce ACTH despite the glucocorticoid excess. Among the possible causes receptor overexpression or lack of receptor down regulation are listed, but some other mechanisms that cause an accumulation of cytokeratin but which do not inhibit cortisol production are also possible [1].

Crooke's cell adenomas [CCA] are a unique subtype of corticotroph adenomas in terms of clinical course and pathology. They are very rare and their incidence is estimated at less than 1% of all pituitary adenomas and from 4.4 to 14% of corticotropinomas [1, 3]. Because of their rarity the management and treatment remain a challenge.

Until now only 80 cases of Crooke's corticotropinomas have been published in literature [1]. According to George et al. [4] it is possible to recognise Crooke's cell adenomas if more than 50% of the cells show Crooke's hyalinisation.

The first three cases were reported in 1981 by Felix et al. [2]. In 2003 George et al. [4] presented the largest series to date of 36 cases of Crooke's cells corticotropinomas. Almost all other patients with this type of pituitary adenoma were described as case reports.

According to Di Ieva et al. [1], 77.2% of Crooke's cells tumours are macroadenomas and 79.2% of them are invasive and resistant to conventional surgery and radiotherapy, with a 66% recurrence rate. Cushing's disease occurs in 75.6% of them. The others are silent ACTH-adenomas.

To date there is no fully effective method of treatment for these tumours. Recent reports suggest that temozolomide, an imidazotetrazine derivative of the alkylating agent dacarbazine, which inhibits DNA replication, can be effective in controlling Crooke's tumours. The use of TMZ in Crooke's corticotropinomas cases was previously described in eight cases of CCA [3, 5–8].

The aim of the study was to present a patient in whom we achieved a complete remission of Crooke's cells pituitary adenoma that lasted for 33 months after cessation of treatment with temozolomide, in relation to data from the literature.

Case report

A 54-year-old man was diagnosed with Cushing's disease five years previously. Since January 2010 he watched the growing signs of hypercortisolism: increasing body weight, hyperpigmentation of the skin, accumulation of fat on the neck, lunar face, atrophy of muscles on the thighs and buttocks, and depressed mood. Laboratory tests showed high ACTH concentrations, loss of circadian cortisol rhythm, elevated urinary cortisol excretion, and lack of cortisol inhibition after 1 and 8 mg of dexamethasone.

The pituitary MRI revealed a 29 × 32 mm tumour located in the sella turcica and suprasellar region.

Within two years the patient underwent three subtotal selective transsphenoidal adenomectomies without retirement of hypercortisolaemia. Progression of the tumour (36 × 33 × 39 mm] with its penetration into both cavernous sinuses together with a compression of the optic chiasm was the reason for the disqualification of the patient to gamma-knife treatment.

Clinical manifestations of hypercortisolism were present throughout the treatment period. Pathological examination of the material obtained during surgical procedures showed polygonal tumour cells with weak nuclear pleomorphism. The vast majority of cells exhibited Crooke's hyaline change (Fig. 1A). The ACTH reactivity was apparent (Fig. 1B), but the other pituitary hormones (growth hormone, prolactin, TSH, FSH, LH, and alpha subunit) were immunonegative. The Ki-67 (MIB-1) labelling index was low, < 1% (Fig. 1C), and scattered neoplastic cells showed weak nuclear p53 immunoreactivity (Fig. 2D). Tumour cells were O^6-methylguanine-DNA methyltransferase (MGMT) immunonegative (Fig. 1E). Electron microscopy showed large polygonal tumour cells packed with the dense masses of cytokeratin filaments. The cells also used to have ovoid or irregular nuclei containing prominent nucleoli. Secretory granules, 200–350 nm in diameter, were not numerous and were displaced to the cell periphery by cytokeratin filaments or remained trapped within the Golgi region (Fig. 1F).

Due to a further progression of the tumour size, another neurosurgical intervention was contraindicated.

At the time of qualification to temozolomide treatment the patient reported weakness of vision in the right eye. MRI of hypothalamic-pituitary area revealed

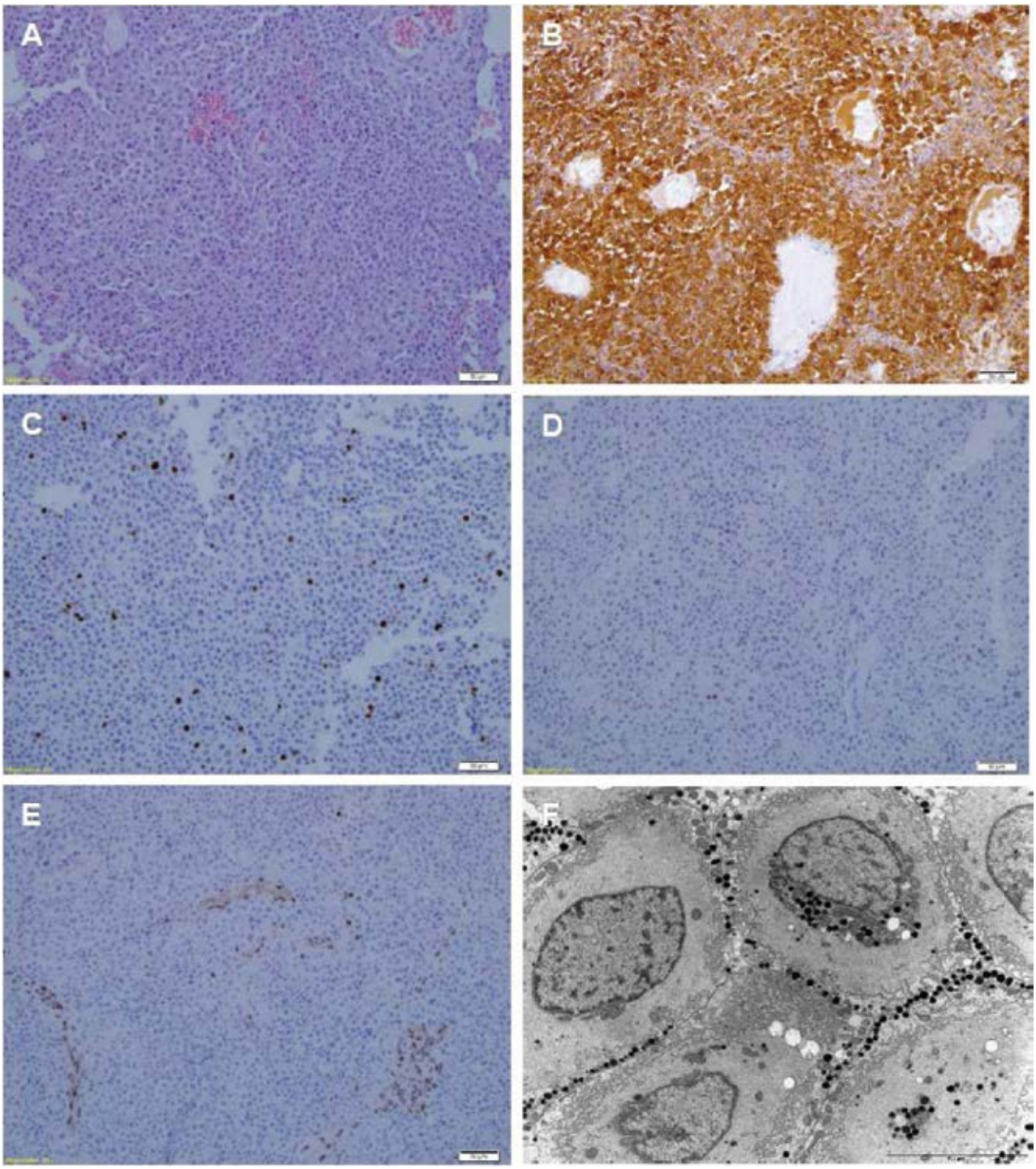

Figure 1. A. *Histology of Crooke's corticotroph adenoma (H&E).* **B.** *Immunopositivity for ACTH in Crooke's cell corticotroph macroadenoma.* **C.** *Immunostaining for Ki-67 antigen: low MIB-1 labelling index (< 1%).* ***D.*** *Low expression of p53 antigen.* **E.** *Negative immunostaining tumour cells for O^6-methylguanine-DNA methyltransferase (MGMT) in the presence of a positive internal control (endothelial cells).* ***F.*** *Ultrastructural features of Crooke's cell adenoma: large cells with excessive accumulation of perinuclear cytokeratin filaments with only a few organelles and variable in shape, electron dense secretory granules displacement to the cell periphery. Original magnification × 9700*

Rycina 1. A. *Histologia gruczolaka kortykotropowego z komórek Crooke'a (H&E).* **B.** *Dodatnie barwienie na ACTH w komórkach makrogruczolaka.* **C.** *Reakcja immunologiczna w kierunku antygenu Ki-67: niski wskaźnik MIB-1 (<1%).* **D.** *Niska ekspresja antygenu p53.* **E.** *Ujemny wynik barwienia w kierunku MGMT w komórkach guza, w obecności dodatniej kontroli wewnętrznej (komórki śródbłonka).* ***F.*** *Ultrastruktura komórek Crooke'a: duże komórki z nadmierną okołojądrową akumulacją włókien cytokeratyny, z kilkoma organellami i przesuniętymi na obwód komórki różnokształtnymi, gęstymi elektronowo ziarnami sekrecyjnymi. Oryginalne powiększenie × 9700*

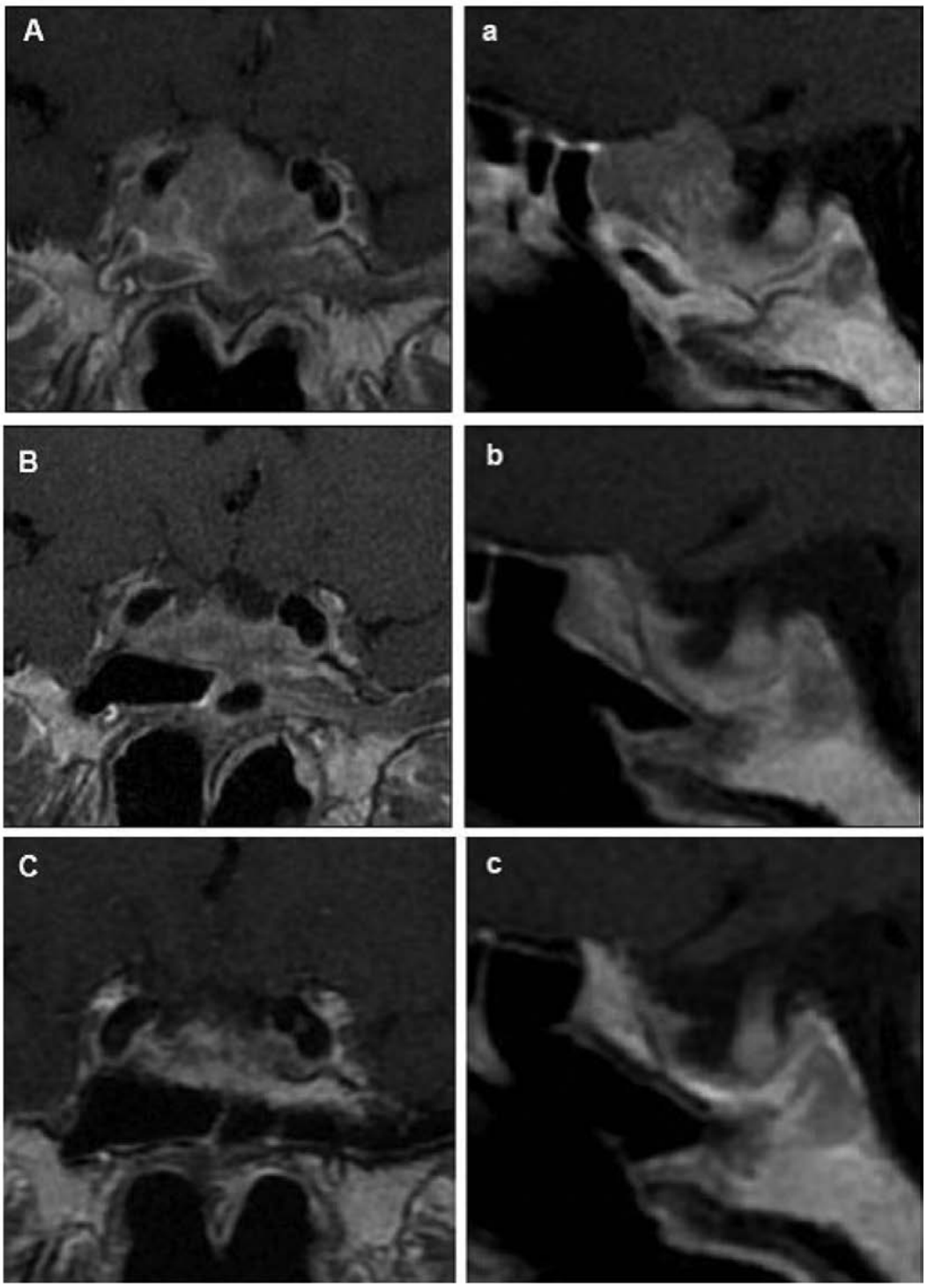

Figure 2. *Coronal and sagittal MRI of the pituitary gland.* ***[A/a]*** *— regrowth of the tumour after third surgery, before TMZ treatment,* ***[B/b]*** *— after 6 courses of TMZ.* ***[C/c]*** *—sustained pituitary adenoma shrinkage after TMZ discontinuation with residual tumour invading right cavernous sinus, signs of secondary "empty sella", pituitary gland placed at the floor of the sella*

Rycina 2. *Projekcja wieńcowa i strzałkowa MRI przysadki.* ***[A/a]*** *— odrost guza po 3 operacji, przed leczeniem TMZ;* ***[B/b]*** *— po 6 kursach TMZ.* ***[Cc]*** *— utrzymująca się redukcja rozmiarów gruczolaka po zakończeniu leczenia TMZ, z pozostałością guza w prawej zatoce jamistej, objawami wtórnego „pustego siodła' i przysadką zlokalizowaną na dnie siodła tureckiego*

the presence of a 23 × 33 × 28 mm (Fig. 2A, a) intrasellar and suprasellar tumour, penetrating to the cavernous sinuses. Compared to previous studies, a progression in tumour size was shown. The residual pituitary was located at the back and moved on to the right side. The tumour reached the optic chiasm and caused its compression from the right side and pressed the basis of the right frontal lobe.

Table I. *Hormonal assessment before and after TMZ treatment*
Tabela I. *Ocena hormonalna przed i po leczeniu TMZ*

Number and date of course	Dose of TMZ	ACTH 8.00 pg/mL (7.2–63.6)	Cortisol 8.00 μg/dL (4.3–22.0)	Cortisol 22.00 μg/dL (3.1–16.7)	Urinary cortisol excretion μg/24h (55.5–286.0)
I/12 — 16. 07 '12	5 × 240 mg	260.6	26.7	22.6	1735
II/8 — 12. 08 '12	5 × 250 mg	177.8	35.6	18.7	757
III/5 — 9. 09 '12	5 × 250 mg	120.3	13.0	13.4	345
IV/4.10 — 8.10 '12	5 × 250 mg	82.4	11.9	8.9	180.4
V/30.10 — 3.11 '12	5 × 250 mg	–	6.9	–	–
VI/27.11 — 1.12 '12	5 × 250 mg	62.6	6.6	3.2	33.0
VII/4.01 — 8.01 '13	5 × 250mg	42.3	4.8	–	57.6
VIII/1.02 — 5.02 '13	5 × 250 mg	40.3	7.3	2.1	50.4
IX/28.02 — 4.03 '13	5 × 250 mg	34.4	10.6	3.8	151.2

Temozolomide was used in a dose of 150 mg/m^2 once a day in the morning (240–250 mg/day) for five consecutive days, with a 23 day interval. The tolerance of treatment was good, ondansetron was used for the prevention of nausea and vomiting. At the same time the patient was treated with ketoconazole 1000 mg/day.

The course of treatment and the parameters of the pituitary-adrenal axis during taking temozolomide are shown in Table I.

After the first cycle of treatment a significant decrease in ACTH level and daily urine cortisol excretion were observed. After the second course of treatment the patient reported an improvement of vision in the right eye and an increase in exercise capacity.

We observed regression of cushingoid features, reduction of swelling, lowering of blood pressure, and decreasing of body weight by 6 kg. After three treatment courses, further decline in plasma ACTH was found together with the reduction of cortisol urinary excretion and normalisation of its concentration in blood without a return of the circadian rhythm.

MRI showed a reduction of intrasellar and suprasellar adenoma size [19 × 30 × 19 mm]. Compared to the previous imaging studies, the part of the tumour penetrating into the anterior cranial fossa, ethmoid cells, and the optic chiasm was smaller. A withdrawal of the optic nerves impression was observed together with a reduction of a mass covering the superior orbital fissure.

After six courses of TMZ normal ACTH and circadian cortisol rhythm returned. Serum cortisol concentration and excretion in daily urine fell below the lower normal range. Ketoconazole was withdrawn.

In the MRI picture there was a further slight decrease of intrasellar and suprasellar tumour mass and also a reduction of its part surrounding the right cavernous sinus (Fig. 2Bb).

During the next three TMZ courses, normal levels of ACTH and a further decline in cortisol levels were observed. Cortisol concentrations in the blood were below the lower limit of normal range with a preserved circadian rhythm at the same time.

After nine courses of temozolomide there was a further regression of the tumour in MRI. A poorly distinguishable part surrounding the right cavernous sinus was present, but intrasellar and suprasellar pathological mass was not found.

Due to persistent five-month remission, TMZ was withdrawn. The results of hormonal evaluation repeated after treatment discontinuation are shown in Table II.

The first evaluation conducted in October 2013 showed sustained complete remission of the disease with normal pituitary-adrenal axis function and normal results in the assay with 1 mg of dexamethasone. Subsequent MRI (2014, 2015) (Fig. 2 Cc) confirmed the characteristics of the secondary empty sella with a small pituitary gland on the right side and sustained tumour regression.

Total remission was maintained for 33 months after the end of chemotherapy with temozolomide.

Discussion

According to many authors [5, 9–15], temozolomide is an efficacious, accessible, easy to use, and well-tolerated medication of low toxicity that can be used for treatment of life-threatening pituitary tumours that are refractory to standard treatment modalities. The general effectiveness of TMZ therapy is approximately 55% for aggressive adenomas and 58% for pituitary carcinomas [9]. Losa et al. [11] have reported that TMZ therapy helped to control the disease (a decrease in tumour

Table II. *Hormonal results after TMZ discontinuation*

Tabela II. *Wyniki badań hormonalnych po zakończeniu leczenia TMZ*

Date	Parameter	Result	Normal range
October 2013	ACTH pg/mL 8.00	36.77	7.2–63.6
	Cortisol μg/dL 8.00	13.8	4.3–22.4
	Cortisol μg/dL 22.00	2.4	3.09–16.66
	Cortisol urine excretion μg/day	99.0	55.5–286
	Cortisol inhibition test after 1 mg DXM ug/dL	0.9	< 1.8
February 2014	ACTH pg/mL 8.00	34.2	< 46
	Cortisol nmol/L 8.00	218	101–536
	Cortisol inhibition test after 1 mg DXM nmol/L	< 28	< 28
July 2014	ACTH pg/mL 8.00	24.9	<46
	Cortisol nmol/L 8.00	191	101–536
February 2015	ACTH pg/mL 8.00	21.6	< 46
	Cortisol nmol/L 8.00	259	101.2–535.2
October 2015	ACTH pg/mL 8.00	35.6	< 46
	Cortisol nmol/L 8.00	240	101.2–535.2

volume of at least 50%) or stabilise it (a reduction in tumour of less than 50% or volume increment of less than 25%) in 80.6% of patients. Based on heretofore publicated reports, Bruno et al. [9] and Li et al. [12] suggest, that TMZ may be a salvage therapy mainly in atypical prolactinomas (73% response rate) and atypical corticotropinomas (60% response rate).

Since 2004, TMZ therapy has been used in approximately 130 patients with atypical adenoma or carcinoma of the pituitary with varying results [5, 9–11, 13–15]. Experience with TMZ treatment in patients with Crooke's cell tumours is limited. The clinical data of the eight patients who have been treated with TMZ due to Crooke's cell tumours presented in the literature to date and those of the ninth patient described in this article are shown in Table 3 [3, 5, 7–9].

Most of the patients in this group, similarly as in the whole reported Crooke's tumour group [1], were female, and they were aged 42 to 60 years. Temozolomide was usually administered in a standard dose of 150–200 mg/m^2 over a period of five days in 28-day cycles. The number of courses of therapy completed by the patients was 9 to 23. The state of most of the patients (88.9%) improved after the therapy, causing remission in four (44.4%) of the patients (two with adenoma and two with carcinoma) and partial regression of the tumour in another four patients (two with adenoma and two with carcinoma). Two of the patients with partial improvement relapsed after eight and nine months of treatment, respectively (Table III).

Four patients with Crooke's tumour(44.4%) achieved long-term and complete remission. In two of the patients who continued to be treated with TMZ remission was maintained for 20 and 26 months, respectively, at the time of publication [3, 7]. In the third patient remission lasted 18 months after the completion of TMZ therapy, and this was the first case of long-term and complete remission of Crooke's tumour after TMZ chemotherapy described in the literature [8]. The patient described in this article has been in remission for 33 months since completing the TMZ treatment.

Atypical pituitary corticotropinomas, which account for approximately 1/3 of tumours treated with TMZ [9, 11, 14], including Crooke's tumours, seem to respond particularly well to this type of treatment. TMZ therapy resulted in stabilising the disease (total remission, partial remission, or lack of progression) in more than 60% of patients [9, 11, 14].

So far, long-term remission after completing TMZ therapy has been reported in six patients including four with corticotropinomas (19 and 30 months after the therapy was completed in two patients with silent corticotropinoma [10] and 18 and 33 months after the treatment in two patients with Crooke's adenoma, respectively) and in two patients with pituitary carcinoma (48 after the treatment in patients with somatotroph carcinoma and after 91 months in patients with GH- and PRL-secreting carcinoma [13]).

Atypical adenomas are defined by having a Ki-67 (MIB-1) proliferation index of 3% or more and extensive nuclear staining for the p53 protein [7]. Among the seven patients with Crooke's tumour (Table III) whose Ki-67 was analysed, an index ≥ 3% was found in four cases, and in the remaining three cases, including our patient, Ki-67 was lower. Similarly, the number of cells with strong p53 protein immunoreactivity was low in four of the tumours examined. Considering the aggressive clinical presentation of the disease, this could indicate a relatively low proliferation potential of Crooke's tumours and can be associated with their better response to TMZ treatment than that of other atypical pituitary tumours.

Likewise, the low proliferation index in the patients with Crooke's tumour has been observed by Di Ieva et al. [1] and George et al. [4]. The mean Ki-67 was 0.7% and there were no statistically essential differences of the index values between invasive and non-invasive tumours [4]. Losa et al. [11] also did not find any correlation between the level of Ki-67 and clinical response to TMZ treatment.

Temozolomide causes DNA damage through methylation of the O6 position of guanine, forming the most potent cytotoxic DNA adducts. O6-methyl-guanine-

Table III. *Published data concerning Crooke's corticotropinomas treated with TMZ, including our patient*
Tabela III. *Opublikowane dane dotyczące gruczolaków Crooke'a leczonych TMZ z włączeniem naszego chorego*

No	Reference	Gender	Age	Tumour type	Cushing's syndrome	Tumour size	Ki67[%]	MGMT	p53 [%]	TMZ Treatment schedule	Number of courses	Results of treatment
1.	Mohammed et al. 2009 [5]	F	43	Adenoma	Yes	Macro	Not performed	Absent	Not performed	150–200 mg/m^2 × 5/28 d	12	Partial tumour regression "improved"
2.	Rotondo et al. 2012 [6]	F	49	Adenoma	yes	macro	5–8	Absent	Not performed	85 mg daily	Not available	Not available
3.	Hirohata et al. 2013 [7]	F	45	Adenoma	Not available	Not available	46,8	Present	3	150–200 mg/m^2 ×5/28 d	11	Partial tumour regression, relapse after 9 months
4.	Asimakopoulou et al. 2013 [8]	F	55	Adenoma	Yes	Macro	1	Not performed	Not performed	150–200 mg/m^2 × 5/28 d	10	Complete remission from 18 months
5.	Our patient	M	54	Adenoma	Yes	Macro	< 1	Absent	< 1	150–200 mg/m^2 × 5/28 d	9	Complete remission from 33 months
6.	Mohammed et al. 2009 [5]	M	60	Carcinoma	Yes	Macro	Not performed	Present	Not performed	150–200 mg/m^2 × 5/28 d	12	Partial tumour regression "improved"
7.	Takeshita A et al. 2009 [3]	F	52	Carcinoma	Yes	Macro	~ 3	Weak	Not performed	150–200 mg/m^2 × 5/28 d	23	Complete remission from 26 month, required GC therapy
8	Hirohata et al. 2013 [7]	F	42	Carcinoma	Not available	Not available	3.4	Absent	10	150-200 mg/m^2 × 5/28 d	8	Partial tumour regression, relapse after 8 months
9.	Hirohata et al. 2013 [7]	F	53	Carcinoma	Not available	Not available	2	Present	< 1	150–200 mg/m^2 × 5/28 d	20	Complete remission from 20 months

DNA methyltransferase (MGMT) is a DNA repair protein that reverses alkylation at the O6 position of guanine by transferring the alkyl group to a sulphur group of cysteine, removes the alkylating adducts induced by TMZ treatment, and provides resistance to TMZ [7]. According to many authors [3, 7, 12, 13, 15], low MGMT expression predicts a better response to temozolomide.

The expression of MGMT in the cells of Crooke's cell tumour was examined in eight out of the nine patients discussed in this article (Table III). MGMT expression was low or non-existing in five of the patients, and it was present in the remaining three patients. Among the three patients who were all in complete remission, one had MGMT expression, one had low expression, and one had none. MGMT also expressed differently in patients with partial remission of the tumour (Table III), which, as stated by some authors [7, 11, 12], would indicate that it is not a reliable marker of the sensitivity of the cells to TMZ.

A prompt re-growth of the tumour after each surgery and the fact that the patient did not qualify for gamma-knife treatment caused our patient to be treated with temozolomide. Similarly to the remaining cases, the patient tolerated the treatment well, and no side effects were observed. The TMZ therapy administered in our patient resulted in a remission of the adenoma, which has been maintained for 33 months since the patient completed the treatment. This patient is the second case of this type that has been described in the literature.

To sum up, corticotroph adenomas and carcinomas, including Crooke's cell tumours, seem to be more responsive to TMZ treatment than other atypical pituitary tumours. MGMT is not always a reliable marker of the sensitivity of the tumour to TMZ. Despite their aggres-

sive clinical presentation, some Crooke's cell adenomas do not always meet the histological criteria of the WHO for atypical pituitary adenomas and are characterised by a low (< 3%) Ki-67 and p53.

Conclusions

Temozolomide can be an effective treatment option in invasive Crooke's cell corticotropinoma.

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