Journal of the Endocrine Society, 2022, **6**, 1–12
https://doi.org/10.1210/jendso/bvab190
Advance access publication 22 December 2021
Case Report

Temozolomide Nonresponsiveness in Aggressive Prolactinomas and Carcinomas: Management and Outcomes

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Abstract

Context: Temozolomide (TMZ) is endorsed as the treatment of choice in aggressive or malignant pituitary adenomas.

Objective: Herein we describe a case of an aggressive prolactinoma that was resistant to TMZ. We performed a literature review of similar nonresponsive, aggressive prolactinomas.

Methods: A 40-year-old woman presented with a giant prolactinoma that required cabergoline, transsphenoidal surgery, and radiotherapy to achieve near-normal prolactin and apparently no residual tumor. A year later, she presented with multiple cranial nerve involvement due to a recurrent tumor extending to the infratemporal fossa. She underwent transfrontal surgery, second radiotherapy, and was started on TMZ. Despite 8 cycles of temozolomide (200 mg/m^2, 5/28-day cycle), she had progressive disease and ultimately succumbed to the disease. PubMed/MEDLINE, Google Scholar, and prior review articles were searched for manuscripts about patients with aggressive prolactinomas who had been treated with TMZ. Data on demography, duration of therapy, and management outcomes were analyzed in those with progressive disease.

Results: We identified 94 cases of patients with aggressive/malignant prolactinomas in the literature who had received TMZ. Progressive disease despite TMZ was present in 36 cases (38%). There was a male preponderance (65%) among these and 40% had aggressive prolactinomas, whereas the rest had carcinomas. Patients received a median of 8 cycles (interquartile range, 3.5-11.5) of TMZ. O6-methylguanine-DNA-methyltransferase (MGMT) immunostaining was negative in 35%. Overall mortality at the time of publication was 40%, at a duration varying from 2 to 20 years from diagnosis.

Conclusion: TMZ resistance in aggressive/malignant prolactinomas is challenging. Progressive disease on optimal TMZ treatment entails the use of newer agents.

Key Words: temozolomide, aggressive prolactinoma, MGMT, temozolomide resistance

Abbreviations: DA, dopamine agonist; ER-α, estrogen receptor α; HRT, hormonal replacement therapy; IQR, interquartile range; MGMT, O6-methylguanine-DNA-methyltransferase; MRI, magnetic resonance imaging; T4, thyroxine; TMZ, temozolomide; VEGF, vascular endothelial growth factor.

Prolactinomas are the most common clinically relevant pituitary tumors. They have a spectrum ranging from microprolactinomas to large, aggressive, and rarely malignant disease. Aggressive prolactinomas are defined as radiologically or histopathologically invasive masses with unusually rapid proliferation or clinically relevant tumor growth despite standard treatment modalities [1]. Clinical behavior of the tumor is regarded as the best marker for aggressiveness [2, 3]. Pituitary carcinomas share multiple histopathological features with aggressive adenomas but are defined only in the presence of distant metastases [2, 4, 5].

Management of aggressive prolactinomas and carcinomas is a challenge. Though there are certain predictors of aggressiveness (male, young, genetic predisposition, lower estrogen receptor α [ER-α]), there are no reliable clinical or histological markers that can delineate aggressive prolactinomas at baseline [3, 4]. Prospective follow-up alone can help in identifying aggressive tumor behavior and malignancy. Surgery is usually resorted to as the second line of therapy, but aggressive prolactinomas fare poorly, with high chances of recurrence [6]. Radiotherapy is the next commonly used modality but interim medical management is required [7].

Received: 6 October 2021. **Editorial Decision:** 16 December 2021. **Corrected and Typeset:** 17 January 2022

Chemotherapy is emerging as the treatment of choice in aggressive prolactinomas, following failure of dopamine agonist, surgery, and radiotherapy. Temozolomide (TMZ) is the agent of choice in such cases [1]. TMZ was first used in a patient with prolactin-producing pituitary carcinoma in 2006 [8], and its use has been reported in more than 350 cases of aggressive and/or malignant pituitary neoplasms to date [9].

Here we report the clinical course, complex management, and outcome of a patient with an aggressive prolactinoma. We reviewed all published cases of aggressive prolactinomas and prolactin-secreting pituitary carcinoma with a documented disease progression despite TMZ therapy (94 TMZ-treated cases including 36 with progression on TMZ).

Case Vignette

A 40-year-old woman presented with headache and blurred vision of the left eye the year preceding presentation. Following normal pubertal development and menarche at age 13 years, she developed secondary amenorrhea at age 28 years. She had no sign of galactorrhea, hirsutism, weight gain, easy bruising, or striae suggestive of endogenous hypercortisolism. The patient intermittently sought medical opinions from various physicians and was prescribed hormone replacement therapy (HRT), but without withdrawal bleed. In the interim, she married and sought a medical opinion for infertility. Eventually, she adopted a child from her sister. At the age of 40 years she presented at our department complaining of headache and blurred vision in her left eye, which were present for 1 year before presentation. There was no family history of pituitary adenomas and she did not show the multiple endocrine neoplasia 1 phenotype. On examination, she had expressive galactorrhea, no hirsutism or acral enlargement. Her visual acuity was diminished (6/36 in her left eye, 6/6 in her right) and she had bitemporal hemianopia. Biochemical assessment revealed a serum prolactin level of 3623 ng/mL (normal range [N] < 25), thyroxine (T4) 7.2 µg/dL (N = 4.8-12 µg/dL), 0800h cortisol 170 nmol/L (N = 170-536 nmol/L), follicle-stimulating hormone 2.3 mIU/L (N = 1.8-12.8 mIU/L), luteinizing hormone 1.5 mIU/L (N = 2.4-12.6 mIU/L), and estradiol 18 pg/mL (N = 12-166 pg/mL). Magnetic resonance imaging (MRI) showed a giant pituitary tumor (Fig. 1A). She was initiated on an increasing dose of cabergoline from 0.5 mg to 4 mg weekly over 3 months. In view of nonsatisfactory reduction both in prolactin (2029 ng/mL) and tumor dimensions, the cabergoline dose was escalated to 5 mg weekly. Repeat MRI scan after 6 months showed a 2.3 × 2.6 × 3.3-cm sellar residue with sphenoidal extension, corresponding to a 56% reduction in adenoma volume from baseline. Two months later, there was a sustained reduction in serum prolactin level (1195 ng/mL) and she continued to remain euthyroid (T4 = 6.9µg/dL) with acceptable morning cortisol (265 nmol/L). Her cabergoline dose was escalated further to 6 mg weekly, leading to a significant reduction in headache frequency and improved

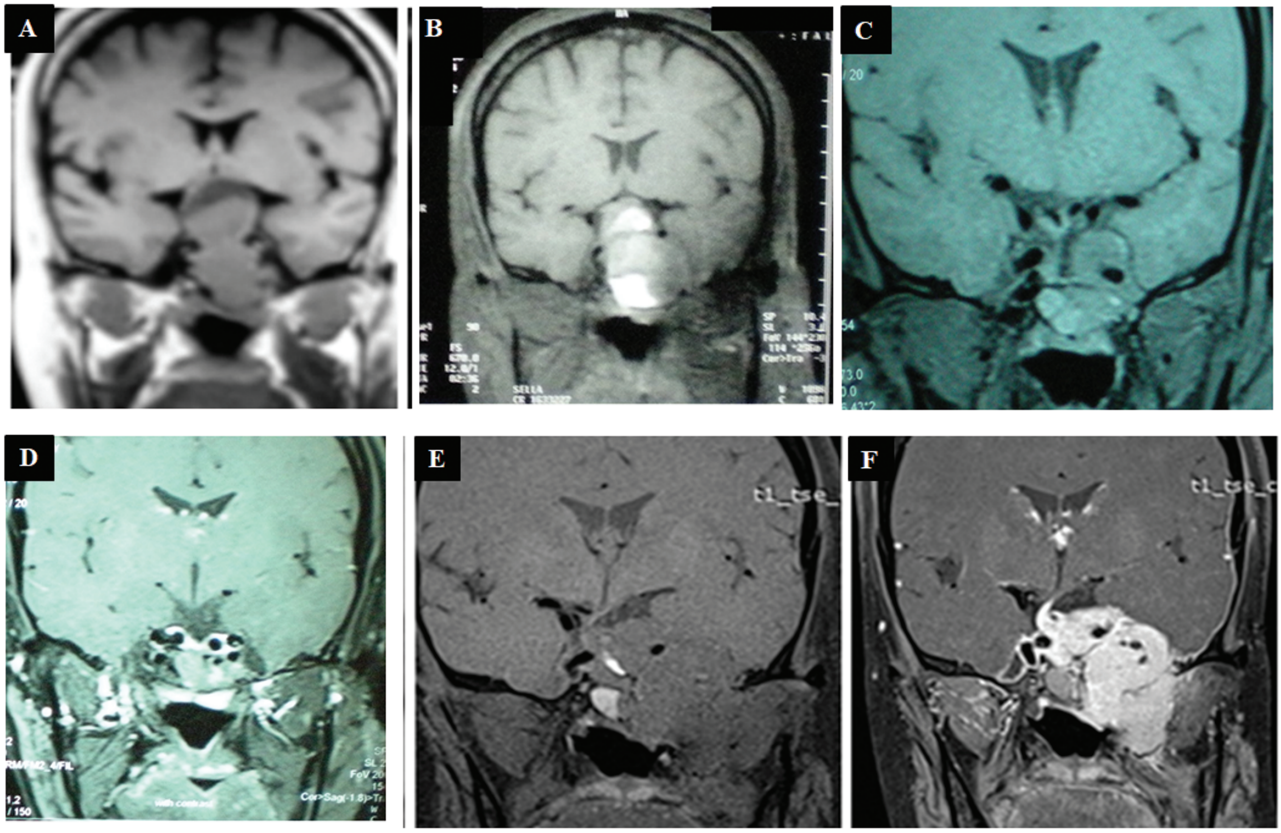

Figure 1. A to F, Panel of magnetic resonance imaging scans of the patient showing A, a 5 × 3 × 3-cm sellar mass extending into the suprasellar and sphenoid regions consistent with a giant macroprolactinoma; and B, showing T1 hyperintense lesions due to pituitary apoplexy in the tumor (hemorrhagic area 3 × 3.4 × 3.3 cm) after 6 months of cabergoline therapy. After transsphenoidal surgery, C, the tumor residue has a right (0.7 × 0.7 cm) and left (1.6 × 1.9 × 1.3 cm) parasellar aspect encasing the left carotid artery and D, shows minimal to absent residue. E and F, One year later an enhancing sellar suprasellar mass (2.1 × 1.9 × 2.7 cm) extends into the left cavernous sinus, middle cranial fossa, pterygopalatine fossa, infratemporal fossa, and left cisternal part of the optic nerve encasing the left cavernous sinus.

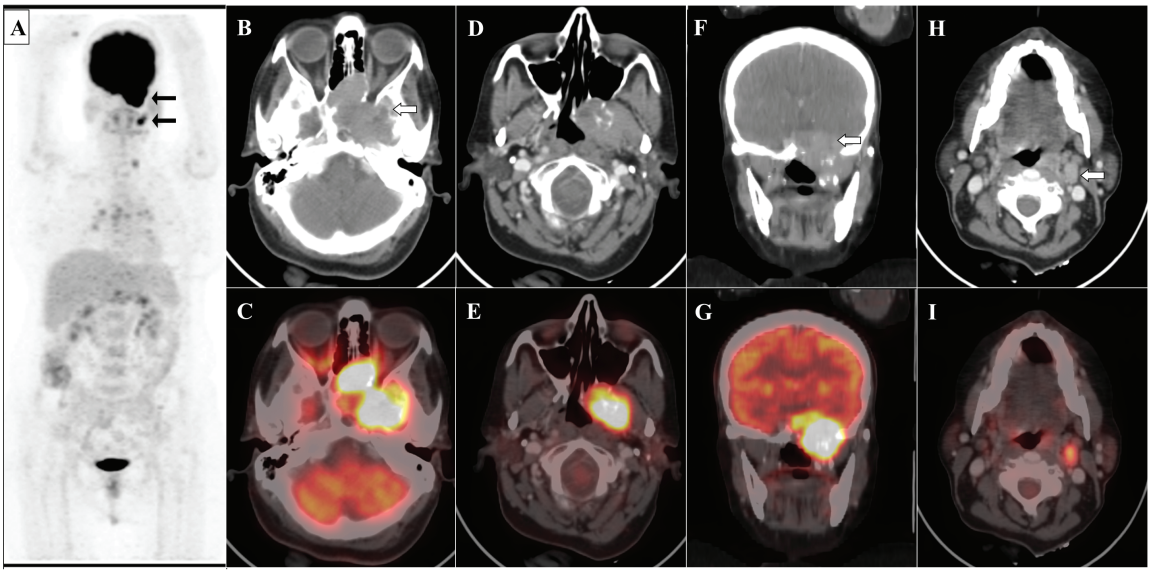

Figure 2. A to I, Maximum intensity projection of the whole-body ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) shows A, abnormal focus of FDG uptake in the region of the base of the skull and in the left cervical region (black arrows). B and C, Transaxial contrast-enhanced CT and fused PET/CT images localized the uptake to a heterogeneously enhancing soft-tissue mass in the left sphenoid region and extending to the pituitary fossa, apex of left temporal bone, the nasal cavity, and apex of left orbit anteriorly with a maximum standardized uptake value (SUV_{max}) of 35.5. D and E, The mass was seen to cause bony erosion of the left greater wing of sphenoid and the left medial and lateral pterygoid plates. F and G, In the coronal CT and fused PET/CT images, the mass has intracranial extension to the left temporal lobe. H and I, There are significant FDG-avid enlarged lymph nodes at cervical level II (white arrow, with SUV_{max} 11.2) and level IV on the left side.

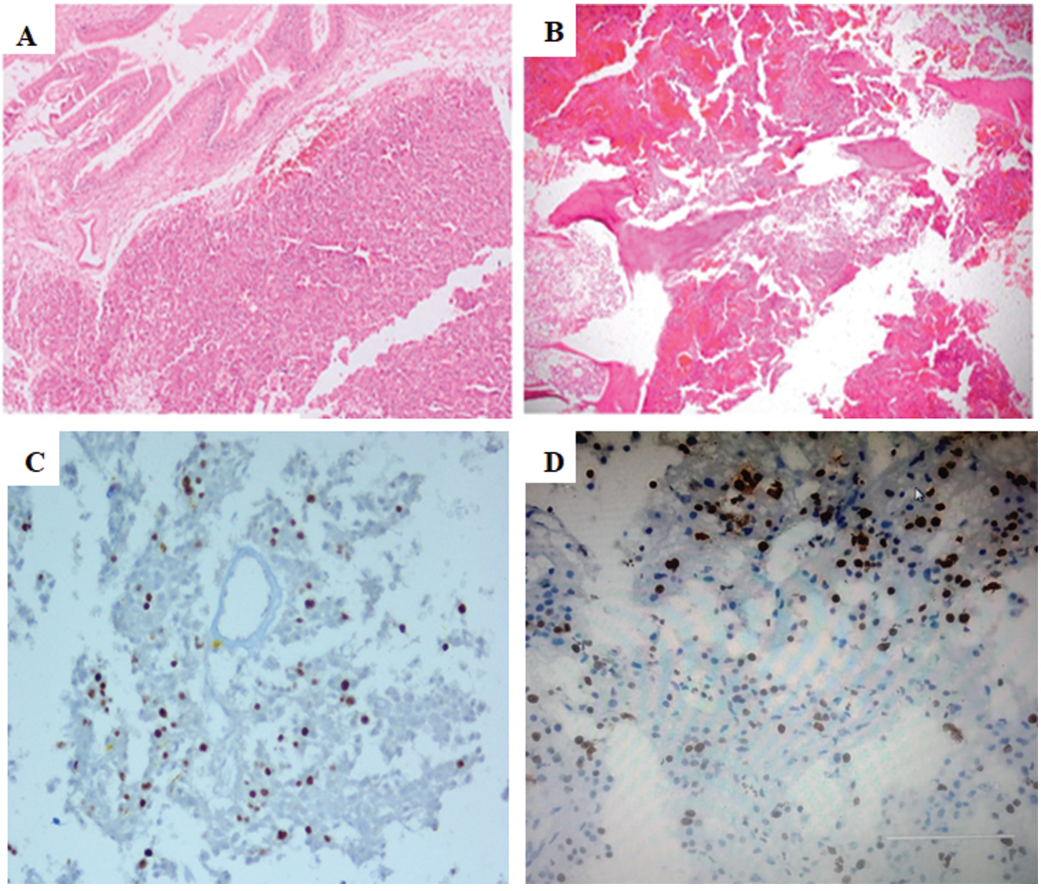

Figure 3. A to D, Panel of photomicrographs depicting A, sphenoid mucosa, and B, bony trabeculae infiltration of the tumor specimen obtained at the second surgery. Ki67 is C, 15% in the first surgery, rising to D, 40% in the second surgery.

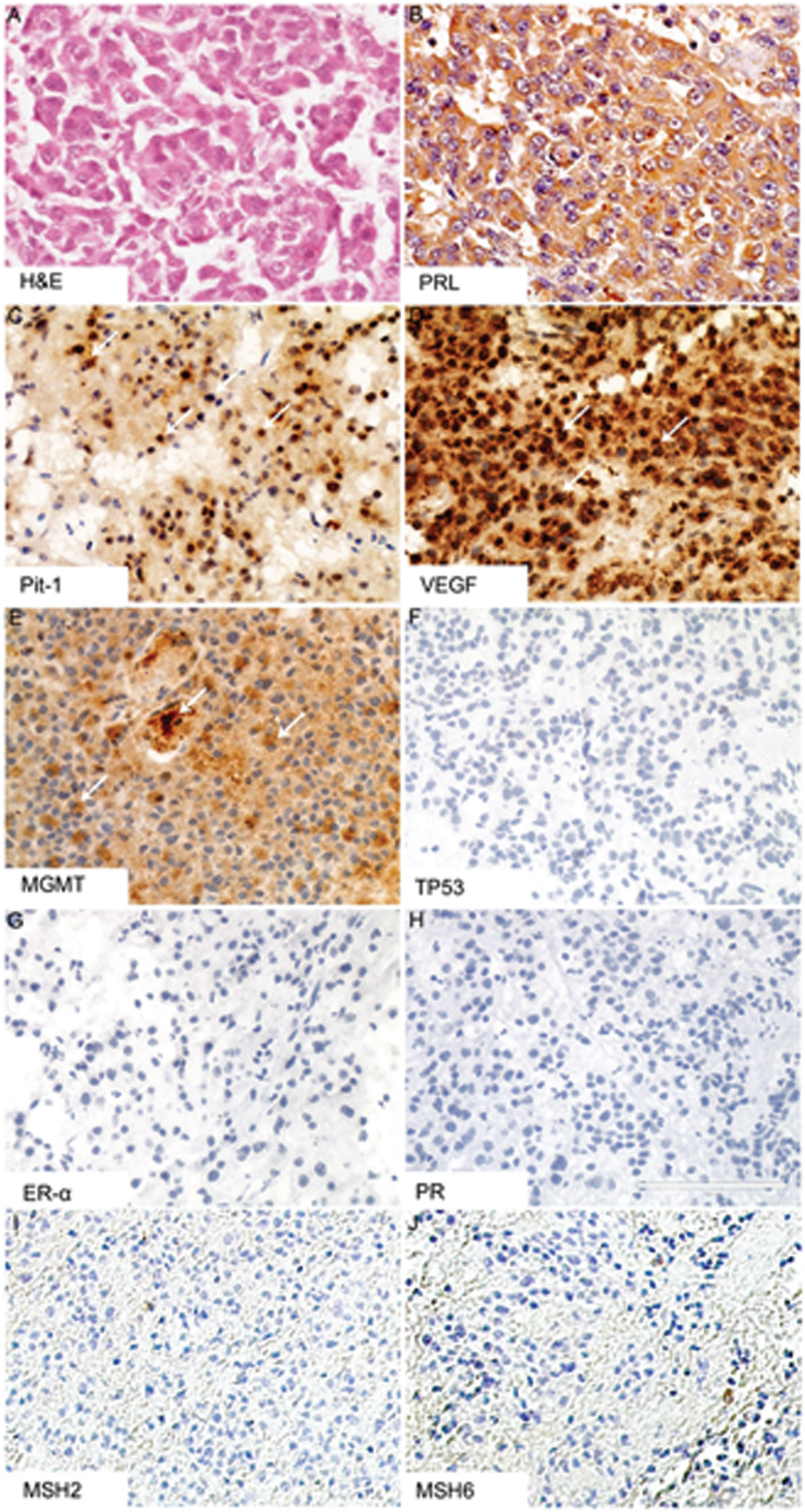

Figure 4. A to H, Hematoxylin-eosin stain (H&E) and A, immunohistochemistry with B, positive prolactin; C, positive Pit-1; D, positive vascular endothelial growth factor (VEGF); E, negative O6-methylguanine-DNA-methyltransferase (MGMT); E, negative p53; G, negative estrogen receptor α (ER-α); H, negative progesterone receptor; and I and J, negative MSH2 and MSH 6 (staining in the sample from the second surgery.

vision. But the patient's prolactin remained high (1184 ng/mL) and amenorrhea persisted. Cabergoline was further increased to a 7-mg weekly dose. However, at 3 months after this dose escalation, an MRI scan showed an increase in tumor dimensions due to a hemorrhagic component, consistent with pituitary apoplexy, although no sudden increase in headache or deterioration in visual parameters was noted (Fig. 1B). Repeat investigations showed persistently elevated prolactin (1328 ng/mL), low T4 (4.62 µg/dL), and baseline cortisol of 350 nmol/L with increase to 482 nmol/L after 1-µg adrenocorticotropin

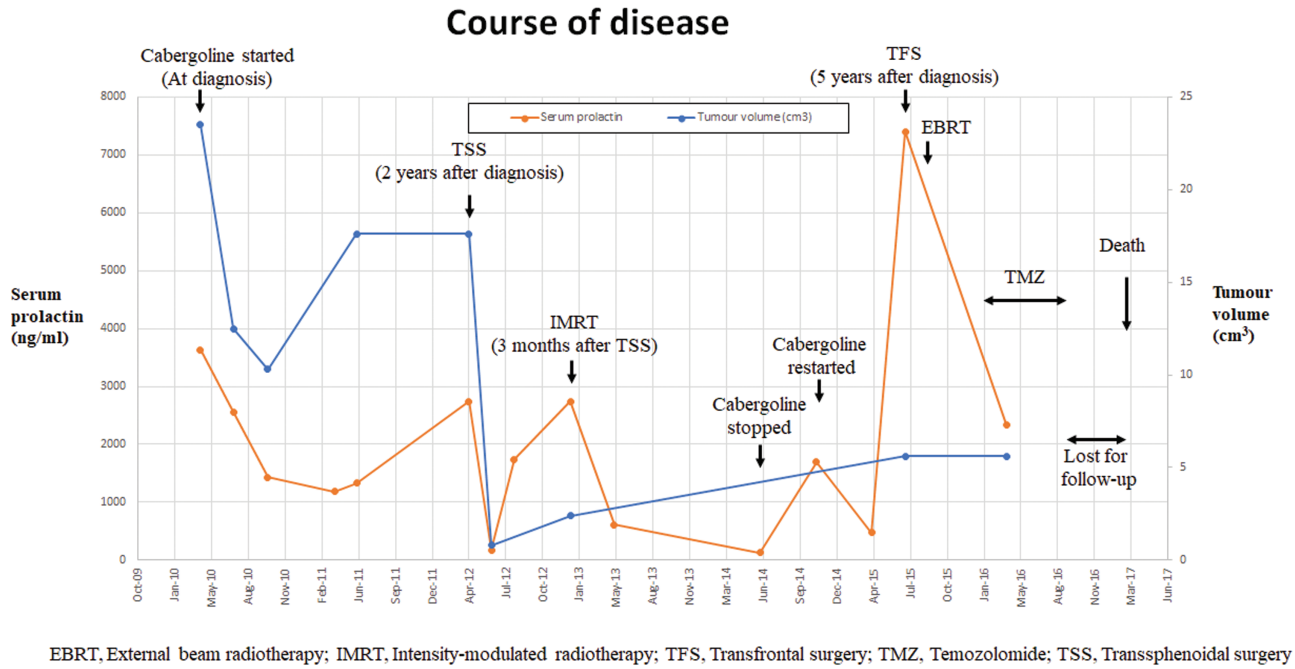

Figure 5. Course and management of the patient using multimodal treatment strategy depicting serial changes in serum prolactin and tumor volume.

stimulation, consistent with a subnormal rise. Cabergoline was continued at a 7-mg weekly dose and she was initiated on levothyroxine 75 µg and oral hydrocortisone 7.5 mg per day. Two years after optimal dopamine agonist (DA) treatment, following a multidisciplinary team discussion, the patient underwent transsphenoidal surgery in view of the partially resistant disease. Histopathology showed a pituitary adenoma with large necrotic areas, mixed inflammatory cells, and few viable tumor cells with hyperchromatic nuclei and moderate eosinophilic cytoplasm, without any evidence of bony invasion. Immunohistochemistry was positive for prolactin. Other hormones could not be assessed because of lack of viable tissue, but Ki67 was high (15%). Two months after surgery her prolactin level reduced to 173 ng/mL, which rose again to 609 ng/mL the next month. Repeat MRI scan showed both left- (1.6 × 1.9 × 1.3 cm) and right-sided (0.7 × 0.7 cm) parasellar tumor tissues (Fig. 1C). In view of the aggressive and resistant nature of her disease, she received fractionated intensity-modulated radiotherapy (54 Gy over 4 wk) with continuation of cabergoline (1-mg weekly dose), levothyroxine, and hydrocortisone. Repeat MRI scan showing a partially empty sella (Fig. 1D) and very mildly elevated prolactin (52 ng/mL) 4 years after the diagnosis were reassuring. Her cabergoline treatment was stopped as she had significant tumor reduction following a combination of medical, surgical, and radiotherapy. Gonadal HRT was prescribed. A year later, she presented with left-sided frontotemporal headache, inability to open her mouth, and difficulty chewing due to a protruding tongue. On examination, she had multiple cranial nerve palsies presenting as left-sided ptosis, diplopia, hemifacial numbness, temporomandibular joint pain, inability to open her mouth, bilateral positive Rinne and left lateralization of Weber test, all suggestive of left-sided third, fourth, fifth, sixth, and eighth cranial nerve involvement. Her visual fields in the left superior and inferior temporal and left superior nasal fields were constricted. Pure tone audiometry showed mixed conductive-sensorineural hearing loss in the left ear and sensorineural hearing loss in her right ear. Her prolactin level was 7400 ng/mL. Repeat MRI scan showed a massive recurrence with left infratemporal extension, requiring redo surgery by the left transfrontal route (Fig. 1E and 1F). ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography showed similar findings as well as a left cervical lymph node (Fig. 2). Fine-needle aspiration from the node was attempted, but it was noncontributory. Cerebrospinal fluid was negative for malignant cytology, but showed a prolactin level of 470 ng/mL. Histopathology revealed a tumor arranged in nest-like pattern with mildly pleomorphic cells and bony infiltration (Figs. 3 and 4). Mitoses were not increased, p53 was negative, but Ki67 was approximately 40%. Immunohistochemistry showed 80% cytoplasmic positivity for prolactin and negative staining for all other anterior pituitary hormones, positivity for Pit-1, vascular endothelial growth factor (VEGF), ER-α, and progesterone receptor. She received second external beam radiotherapy (50 Gy) to the pituitary and infratemporal fossa following the second surgery. TMZ was initiated at 150 mg/m^2 for 5 days every 28 days followed by a 200-mg/m^2 dose from the second cycle onward, for 8 cycles. However, the patient continued to deteriorate and a had weight loss of 16 kg over a 2-year period. Visual acuity also deteriorated to blindness possibly due to radiation-induced optic neuritis. Her prolactin after the third cycle of TMZ remained high at 2341 ng/mL and MRI scan showed bilateral tortuous optic nerves, sagging, and atrophic optic chiasma with cerebrospinal fluid herniation to the nasal cavity. O6-methylguanine-DNA-methyltransferase (MGMT) was strongly positive and MSH2, MSH6 immunohistochemistry were negative. Bevacizumab therapy was suggested in view of the strong VEGF expression in the tumor tissue and also the radiation-induced optic neuritis (Fig. 4). However, the patient could not afford this treatment and hence was given prednisolone 1 mg/kg/week for 3 weeks but did not show a statistically significant response. Whole-exome sequencing of peripheral blood DNA did not reveal any pathogenic variants in *MEN1*, *AIP*, *CDKN1B*, or *SDHx*. A heterozygous be-

Table 1. Literature review of all cases with aggressive prolactinomas or prolactin-secreting carcinomas with resistance to temozolomide therapy (documented progressive disease)

Serial No.	Author/y	No. of nonresponders/ No. of patients	Age at diagnosis, y	Sex	APA/PC	Ki67/p53	MGMT	MSH2/MSH6/ MLH/MGMT promoter methylation	TMZ dose	Cycles of TMZ	Final outcome
1.	Elbelt[a]/2020 [13]	6/18	50 ± 13	39% F	72% APA 18% PC	15 (9-21)/ NA	Minimal expression in 3 tumors	Promotor methylation negative in 29% tumors	150 (145-200)	7 (4-19)	Disease progression in 33% patients at end of TMZ therapy and in 55% at median 30 mo follow-up
2.	Kasuki/2020 [14]	1	52	M	PC (carcinomatous meningitis)	2%/ p53+	NA	NA	300 mg/d in first cycle 400 mg/d subsequently	8	Thrombocytopenia Death 20 y after diagnosis Progressed during first course of TMZ
3.	Santos-Pinheiro/ 2019 [15]	3/4	81	F	PC (dura, lung)	Done in 2 samples Ki67 16%, 25%	Done in only 1 (-ve)	NA	NA	TMZ on recurrence NA	Malignant transformation in 12 y Death < 13 y from diagnosis Progressed during first course of TMZ
4.	Santos-Pinheiro/ 2019 [15]		25	M	PC (dura, bone, liver)				NA	TMZ at diagnosis; NA	Malignant transformation in 2 y Death < 3 y from diagnosis Progressed during first course of TMZ therapy
5.	Santos-Pinheiro/2019 [15]		57	F	PC (bone, liver)				TMZ on recurrence (CAPTEM) capecitabine 1500 mg/m^2 in divided doses 2×/d, d 1-14, and TMZ 100 mg/m^2, d 1-14 of 28-d cycle for 6 cycles	6	Malignant transformation in 6 y Immunotherapy
6.	Bilbao/2017 [16]	1	66	M	PC (liver, LN, lung, vertebral mets)	15%/ weak +	NA	NA	200	24 cycles Recurrence noted 4 mo after discontinuation Restarted with 150 mg/m^2 for 7 d every 14 d 3 cycles	Hyperglycemia, needing insulin therapy in first instance Progression and death after 3 cycles in second instance Progression during second course

Table 1. Continued

Serial No.	Author/y	No. of nonresponders/ No. of patients	Age at diagnosis, y	Sex	APA/PC	Ki67/p53	MGMT	MSH2/MSH6/ MLH/MGMT promoter methylation	TMZ dose	Cycles of TMZ	Final outcome
7.	McCormack[a]/2018 [2]	9/40 (25 APA, 15 PC)	42.7 ± 16.2 44.7 ± 15.1 (NA separate)	35.5% F 37.5% F (NA separate)	NA separate	≥ 3% in 47% patients (NA separate)	Low MGMT in 63% Low MGMT in 65% (NA separate)	-	150-200 mg/ m^2 in 93% patients (5/28) (NA separate)	24 received second instance of TMZ treatment Of these 61.1% (11/18) showed progressive disease (NA separate)	Disease progression in 24% Median time to progressive disease being 12 mo (NA separate) Clinically relevant ADR in 21% patients Cytopenias, fatigue, N/V, SNHL Mortality in 28% APT, 42.5% PC Median duration 11 y from diagnosis
8.	Losa[a]/2016 [17]	1/5	NA	NA	NA	NA	NA	NA	NA	NA	Progressive disease
9.	Bengtsson/2015 [18]	5/9	22	M	APA (MEN-1)	8	90	MMR 2,6 +	150-200	15	110 mo for aggressive growth Progression during second course after initial response obtained in first course (12-mo TMZ) Death 26 mo after stopping TMZ
10.	Bengtsson/2015 [18]		68	M	APA	30	9	MMR 2,6 +	150-200	1	156 mo for aggressive growth
11.	Bengtsson/2015 [18]		23	M	APA	41	100	MMR 2,6 +	150-200	4	30 mo for aggressive growth Progressed during first course of TMZ therapy Death 8 mo after stopping TMZ
12.	Bengtsson/2015 [18]		55	M	APA	10	20	MMR 2,6 +	150-200	11	36 mo for aggressive growth Progressed during second course of TMZ therapy after initial response Death 12 mo after stopping TMZ

Table 1. Continued

Serial No.	Author/y	No. of nonresponders/ No. of patients	Age at diagnosis, y	Sex	APA/PC	Ki67/p53	MGMT	MSH2/MSH6/ MLH/MGMT promoter methylation	TMZ dose	Cycles of TMZ	Final outcome
13.	Bengtsson/2015 [18]		32	F	PC, (LN, brainstem, skeletal mets)	20	50	MMR 2,6 +	150-200	14	192 mo to metastases Progressed likely during first course of TMZ Death 16 mo after stopping TMZ
14.	Bruno/2015 [19]	1	78	M	PC (Brain mets)	10	<10%	NA	140 mg/d	1	Death 2 y after diagnosis
15.	Hirohata/2013 [20]	1/5	49	F	APA	3.9	-ve	MSH 6 score 0	150-200	3	NA Progressed during first course of TMZ therapy
16.	Zemmoura/2013 [21]	1	54	M	PC (jugulo-carotid LN, leptomeningeal)	NA	NA	NA	200	5	TMZ with carboplatin Death 16 y after diagnosis Progressed despite first course of TMZ alone followed by second course of TMZ with carboplatin
17.	Phillips/2012 [22]	1	25	M	PC (dural-based right temporal mass	23 24.8% with 60% p53 positivity	NA	NA	350 mg	5 d only	Death 2.5 y (31 mo) after diagnosis Progression likely during first course of TMZ
18.	Raverot/2010 [23]	3/4	52	M	APA	2	30	No MGMT promotor methylation	150-200	8	NA Progression likely during first course of TMZ
19.	Raverot/2010 [23]		54	M	PC (NA)	7	-ve	Promotor methylation in 8.5%	150-200	5	NA Progression likely during first course of TMZ
20.	Raverot/2010 [23]		30	F	PC (NA)	30	100	No promotor methylation	150-200	3	NA Progression likely during first course of TMZ
21.	Murakami/2011 [24]	1	60	F	PC (intraventricular)	Varying from 14.4% to 18.7% (5× intervened)	-ve	MSH6 initially + ve, later became -ve	200	10	Progression during second course after initial response to TMZ (first 10 cycles) Failed combination therapy with carboplatin and etoposide Died of multiorgan failure and sepsis

Table 1. Continued

Serial No.	Author/y	No. of nonresponders/ No. of patients	Age at diagnosis, y	Sex	APA/PC	Ki67/p53	MGMT	MSH2/MSH6/ MLH/MGMT promoter methylation	TMZ dose	Cycles of TMZ	Final outcome
22.	Losa/2010 [25]	1/2	62	M	APA	9	-ve	No promotor methylation	150-200	12	Progressive disease Required redo surgery (right CN III palsy) Treated with pasireotide Initial response (during first 6 cycles) followed by progression (during last 6 cycles)
23.	Present case	1	40	F	APA with malignant potential (multiple lower CN palsies)	15% to 40% / p53 negative	90	MSH 2,6 negative	150-200	8	Progressive disease No adverse events Advised bevacizumab (unaffordable) Death 8 y after diagnosis Progressed during first course

Abbreviations: -ve, negative; +ve, positive; ADR, adverse drug reactions; APA, aggressive pituitary tumor; CN, cranial nerve; F, female; LN, lymph node; M, male; MGMT, O6-methylguanine-DNA-methyltransferase; MMR, mismatch repair; NA, not available; N/V, nausea/vomiting; PC, pituitary carcinoma; SNHL, sensorineural hearing loss; TMZ, temozolomide.
[a]Individual patient data or data of patients with progressive disease not separately available.

nign missense variant was noted in neurofibromatosis type 2 (*NF2*) (c0.1231C > T; p.Arg411Cys), which was also found in her brother's germline DNA, but neither of them had signs of neurofibromatosis type 2. The patient's disease was progressive, and she succumbed 8 years after first diagnosis as a result of inanition. Her course of management and treatment response are summarized in Fig. 5.

Literature Review

"*Prolactinoma*" or "*pituitary neoplasms*" and "*temozolomide*" were used as terms for a PubMed/MEDLINE literature search yielding 117 results. Other databases such as Google Scholar and prior review articles were also searched [10-12]. These were reviewed individually to identify case reports or series that provided details of patients with prolactin-secreting tumors who received TMZ therapy; 94 such cases were identified. Of the 94 prolactinomas, 36 patients (38%) had documented progressive disease (defined on the basis of RECIST criteria) despite TMZ therapy (Table 1) [2, 13-25]. Studies lacking individual patient data were not included in the statistical analysis [2, 13, 18]. There was an overall male preponderance (65%) and 60% had pituitary carcinomas, whereas the rest had aggressive prolactinomas. Ki67 index (> 3%) was present in all but 2 cases [14, 23]. MGMT immunostaining was negative in 35% patients and the median staining was 50% (interquartile range [IQR], 15-95) (n = 14). MSH2 and 6 were analyzed in only a handful of reports [18, 20, 24]. TMZ was administered to these patients in standard doses (150-200 mg/m^2) for a median of 8 cycles (IQR, 3.5-11.5). There was a 40% mortality rate (with median duration between diagnosis and death of 8 y [IQR, 2.5-13] based on data available), all in patients with malignant prolactinomas including our patient with aggressive prolactinoma.

Discussion

It is believed that pituitary carcinomas develop along a continuum of disease from benign to aggressive adenomas to carcinoma [26]. The sequential tumorigenesis model is characterized by transformation from adenoma to aggressive disease/carcinoma and is more common than the de novo tumorigenesis model, which chronicles the direct development of an aggressive neoplasm from a normal pituitary cell [27]. The clinical course of our patient was in line with the sequential tumorigenesis model. Her disease showed an aggressive behavior with emergence of DA resistance, apoplexy, and tumor regrowth requiring multimodality therapy. Four years after her initial diagnosis, she presented with a massive recurrence in the form of an invasive and proliferative mass, necessitating transcranial surgery, external beam radiotherapy, and TMZ. However, she failed to respond to TMZ and succumbed to her disease.

Clinical pointers to aggressive disease include male sex, young age (< 20 years), germline mutations (*MEN1*, *AIP*), lack of response to DA sometimes after an initial good response, low ER-α expression, epidermal growth factor receptor, VEGF, and transforming growth factor-β positivity [3, 6, 28]. Our patient had low ER-α and intense VEGF positivity. Markers of atypical histology, including high Ki67 (> 3%), mitotic index (> 2), and high p53, although often present, do not reliably identify pituitary carcinomas, as malignant potential may be seen even in cases with lower values of these indices. The definition of carcinoma depends on the demonstration of distant metastases [2, 14, 22, 23]. Resistance to standard doses of DAs is found in up to 15% to 20% of macroprolactinomas on cabergoline [29, 30]. The usual effective dose of cabergoline is 1.5 to 2 mg weekly, but doses up to 3.5 mg weekly are used in more resistant cases or those with giant prolactinomas [31]. In our patient, the dose was escalated to 7 mg/week, which was well tolerated, but her disease was resistant and there was tumor regrowth after an initial 55% reduction from baseline.

Surgery is usually the next line of management, especially in situations such as an apoplectic event, cystic degeneration, or DA resistance, followed by radiotherapy [6]. Our case was first operated on because of partial DA resistance and pituitary apoplexy. At this stage, it was a radiologically invasive and proliferative tumor that evolved to one with much more radiological invasion (infratemporal fossa) and higher Ki67 (40%) at the second surgery. The lymph node might have been metastatic disease, but in the absence of unequivocal demonstration of pituitary tissue or prolactin positivity in it, it was not termed as a metastasis. Nevertheless, the patient was managed as having aggressive/malignant disease, considering the fact that aggressive tumors and carcinomas display similar clinical, radiological, histopathological behavior and are both characterized by premature mortality [4].

TMZ is currently used for aggressive pituitary adenomas, with improved overall survival, and acts by alkylation/methylation of DNA [32]. This is normally counteracted by MGMT. Therefore, an absent MGMT in tumor cells aids cytotoxicity by failing to repair alkylation induced by TMZ and a functional MGMT system causes TMZ resistance [33, 34]. However, if MGMT function is impaired, the cell employs the mismatch repair pathway using MSH2, MSH6, and MLH1 or the base-excision repair process. In our patient, MGMT was positive and MSH2, MSH6 negative, which were possibly responsible for her poor response to TMZ. The literature review revealed absent MGMT expression in 35% of prolactinomas that progressed despite TMZ therapy. This suggests that low or absent MGMT may not always predict response to TMZ in a given tumor. The more prudent approach would be to initiate TMZ and monitor response after at least 3 cycles, irrespective of MGMT status.

TMZ resistance may be primary or arise later in the course of treatment because of selective elimination of sensitive cells and the persistence of resistant cell populations in a heterogeneous tumor [6, 33]. The optimal treatment duration using TMZ is not defined although the recent European Society of Endocrinology guidelines suggest at least 6 to 12 cycles for better outcomes and survival benefit [35]. The index patient's prolactin dropped somewhat after the second surgery, second radiotherapy, and 3 cycles of TMZ treatment, but she died after 8 cycles. Our literature review revealed a higher rate of progressive disease (38%) for aggressive/malignant prolactinomas than in the European Society of Endocrinology survey (24%); the exact reason for this slightly higher rate is not known [2].

Outcomes with TMZ are encouraging; however, it is very difficult to predict which tumor will be aggressive or malignant. Hence the best time of treatment initiation is still questionable [36]. Evidence suggests a better efficacy of concurrent administration of radiotherapy with TMZ, but our patient did not

demonstrate this benefit. The fact that earlier administration of the drug in her case could have yielded better results is plausible. In view of the recent proposition to classify invasive and highly proliferative (Ki67 > 10%) tumors as having malignant potential [37], our patient could have, in retrospect, been initiated with TMZ earlier without discontinuation of the DA [38].

Certain experimental therapies have been proposed to be useful in resistant prolactinomas. ER is demonstrable in 60% to 90% of prolactinomas [3]. The ER antagonist fulvestrant has had beneficial effects in prolactinoma cell lines, while selective estrogen receptor modulators like tamoxifen, raloxifene, and anastrozole have also been tried in clinical settings [39-42]. It is unclear whether in our case the temporal association between initiation of HRT and aggressive growth has a causal relationship. Because the disease already showed aggressive potential (Ki67 15% at first operation, need for surgery, radiotherapy, and resistance to cabergoline), the rapid tumor growth was most likely due to the progressive and aggressive nature of her disease rather than the HRT. Epidemiological studies do not show an association between HRT or oral contraceptives and the development of prolactinomas [5]. Bevacizumab, an inhibitor of the VEGF pathway, has been successfully used in a couple of case reports of corticotroph pituitary carcinomas [43] and 14 cases of aggressive pituitary tumors [44, 45]. It has also been used successfully in radiation-induced optic neuritis [46]. We offered bevacizumab to the patient following demonstration of VEGF positivity and optic neuritis, but cost was the prohibitive factor for use.

Conclusion

The present case demonstrates the utility of early recognition of aggressive prolactinomas, especially those with malignant potential (invasive and highly proliferative). Multimodality therapy is usually the norm. Literature review suggests that TMZ is an efficacious agent in the treatment armamentarium of such challenging tumors, but other treatment options are eagerly awaited for patients with progressive disease during TMZ therapy.

Acknowledgment

We are grateful for all the colleagues who contributed to the patient's care.
Written consent for participation was obtained from the husband of the patient as she died during the course of treatment.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Author Contributions

L.D., A.R., P.S., and P.D. cared for the patient. P.S. performed both surgeries under the guidance of late Prof K.K.M. C.K.A. provided radiological and A.S. provided scintigraphic expertise. A.R. and R.S. performed the immunohistochemical analyses and B.D.R. provided histopathological expertise. L.D. drafted the initial version of the manuscript, which was edited by P.D. and M.K. All authors have read and approved the final version of the manuscript.

Disclosures

The authors have nothing to disclose.

Data Availability

Data sharing is not applicable to this article, because no data sets were generated or analyzed during the present study.

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