Temozolomide Nonresponsiveness in Aggressive Prolactinomas and Carcinomas: Management and Outcomes

Liza Das,1,* Ashutosh Rai,2,* Pravin Salunke,3 Chirag Kamal Ahuja,4 Ashwani Sood,5,6 Bishan Dass Radotra,9 Ridhi Sood,6 Mártá Korbonits,7,8 and Pinaki Dutta1,6

1Department of Endocrinology, Postgraduate institute of Medical Education and Research, (PGIMER), Chandigarh 160012, India
2Department of Endocrinology, PGIMER, Chandigarh, India, Newton fellow Barts and the London school of Medicine
3Department of Neurosurgery, PGIMER, Chandigarh 160012, India
4Department of Radiology, PGIMER, Chandigarh, India
5Department of Nuclear Medicine, PGIMER, Chandigarh 160012, India
6Department of Histopathology, PGIMER, Chandigarh 160012, India; and
7Centre for Endocrinology, William Harvey Research Institute, Barts and The London School of Medicine, Queen Mary University of London, London E1 4NS, UK

Correspondence: Pinaki Dutta, MD, DM, Department of Endocrinology, 1012, Nehru Extension Block, PGIMER, Chandigarh 160012, India. Email: drpinakidutta12@gmail.com.
*These authors are co-first authors of this work.

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/m², 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, 3.5-11.9) 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.
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 36% 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 = 6.9 µg/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 hypointense 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.](image-url)
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.
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 adrenocorticotropic

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.)
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). 18F-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/m² for 5 days every 28 days followed by a 200-mg/m² dose from the second cycle onward, for 8 cycles. However, the patient continued to deteriorate and 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 vari-ants in MEN1, AIP, CDKN1B, or SDHx. A heterozygous be-
| Serial No. | Author/y                | No. of nonresponders/No. of patients | Age at diagnosis, y ± | Sex | APA/PC                      | Ki67/p53 | MGMT                              | TMZ dose | Cycles of TMZ | Final outcome                                                                 |
|-----------|-------------------------|-------------------------------------|------------------------|-----|-----------------------------|----------|-----------------------------------|----------|----------------|-------------------------------------------------------------------------------|
| 1.        | Elbelt/2020 [13]        | 6/18                                | 50 ± 13                | F   | 39% F                       | 72% APA  | 18% PC                            | 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        | NA             | 300 mg/d in first cycle 400 mg/d subsequently                                 | 8        | Thrombocytopenia Death 20 y after diagnosis                                   |
| 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                                                          | NA       | Malignant transformation in 12 y Death < 13 y from diagnosis                   |
| 4.        | Santos-Pinheiro/2019 [15] | 25                                 | 25                     | M   | PC (dura, bone, liver)       | NA       | TMZ at diagnosis; NA              | NA        | NA             | Malignant transformation in 2 y Death < 3 y from diagnosis Progressed during first course of TMZ therapy |
| 5.        | Santos-Pinheiro/2019 [15] | 57                                 | 57                     | F   | PC (bone, liver)             | NA       | TMZ on recurrence (CAPTEM) capecitabine 1500 mg/m² in divided doses 2x/d, d 1-14, and TMZ 100 mg/m², 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/m² 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 |
| Serial No. | Author/s | Year | 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/2018 [2] | 9/40 | 42.7 ± 16.2/44.7 ± 15.1 | 35.5% F/37.5% F (NA separate) | NA separate | ≥ 3% in 47% patients (NA separate) | Low MGMT in 63% patients (NA separate) | - | 150-200 mg/m² 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 Progressive disease 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 | 150-200 | 15 | |
| 8.        | Losa/2016 [17] | 1/5 | NA | 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 | |
| 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 | |
| Serial No. | Author/y No. of nonresponders/No. of patients | Age at diagnosis, y | Sex | APA/PC | Ki67/p53 | MGMT | MSH2/MSH6/MLH1/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] | 78 | M | PC (Brain mets) | 10 | <10% | NA | 140 mg/d | 1 | Death 2 y after diagnosis |
| 15.        | Hirohata/2013 [20] | 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] | 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] | 25 | M | PC (dural-based right temporal mass) | 23 | 24.8% with 60% p53 positivity | NA | NA | 350 mg | 5 d only |
| 18.        | Raverot/2010 [23] | 52 | M | APA | 2 | 30 | No MGMT promoter methylation | 150-200 | 8 | NA Progression likely during first course of TMZ |
| 19.        | Raverot/2010 [23] | 54 | M | PC (NA) | 7 | -ve | Promoter 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 promoter methylation | 150-200 | 3 | NA Progression likely during first course of TMZ |
| 21.        | Murakami/2011 [24] | 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/MGMT promoter methylation | TMZ dose | Cycles of TMZ | Final outcome |
|------------|----------|----------------------------------|-------------------|-----|--------|---------|------|-------------------------------------|----------|-------------|---------------|
| 22.        | Losa/2010 [25] | 1/2                             | 62               | M   | APA    | 9      | -ve  | No promoter 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 diagnosisProgressed 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.

*Individual patient data or data of patients with progressive disease not separately available.
nign missense variant was noted in neurofibromatosis type 2 (NF2) (c.0.1231C>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 pro-
gressive, and she succumbed 8 years after first diagnosis as a
result of inanition. Her course of management and treat-
ment 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 tu-
more who received TMZ therapy; 94 such cases were identi-
fied. Of the 94 prolactinomas, 36 patients (38%) had docu-
mented progressive disease (defined on the basis of RECIST
criteria) despite TMZ therapy (Table 1) [2, 13-23]. Studies
lacking individual patient data were not included in the sta-
tistical analysis [2, 13, 18]. There was an overall male prepon-
derence (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/m²) 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 con-
tinuum of disease from benign to aggressive adenomas to
carcinoma [26]. The sequential tumorigenesis model is char-
acterized by transformation from adenoma to aggressive
disease/carcinoma and is more common than the de novo
tumorigenesis model, which chronicles the direct develop-
ment 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 ag-
gressive 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 radiother-
apy, 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 re-
sponse, low ER-α expression, epidermal growth factor recep-
tor, 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 po-
tential may be seen even in cases with lower values of these
indices. The definition of carcinoma depends on the demon-
stration 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 ef-
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 pitu-
itary 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, consid-
ering 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 alklylation induced by
TMZ and a functional MGMT system causes TMZ resis-
tance [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 nega-
tive, which were possibly responsible for her poor response
to TMZ. The literature review revealed absent MGMT ex-
pression 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 hetero-
genous 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, sec-
ond 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 admin-
istration of radiotherapy with TMZ, but our patient did not
Efficacy of the final version of the manuscript. L.D. drafted the initial version of the manuscript, which was

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 [3]. Bevacizumab, an inhibitor of the VEGF pathway, has been successfully used in a couple of case reports of corticotrop 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.

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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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