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B Zampetti and others | Temozolomide in a macroprolactinoma

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Effective long-term temozolomide rechallenge in a macroprolactinoma

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Summary

We describe the 20-year course of a 63-year-old male with a macroprolactinoma that acquired resistance to treatment and aggressive behavior after a 4-year successful treatment with cabergoline. He was submitted to multiple surgical resections by a skilled surgeon, fractionated radiotherapy and was eventually treated with temozolomide. After a first 6-month standard cycle, a relapse occurred and he was treated again successfully.

Learning points:

- Prolactinomas are the most frequent type of pituitary adenoma.
- They usually have a benign course.
- In most cases dopamine-agonist drugs, mainly cabergoline, are first-line (and usually only) treatment.
- Occasionally prolactinomas can have or acquire resistance to treatment and/or aggressive behavior.
- Temozolomide (TMZ), an oral alkylating drug, can be effective in such aggressive tumors.
- Multimodal treatment (surgery, radiation, cabergoline and TMZ) is warranted in aggressive pituitary tumors.
- We describe here successful rechallenge with TMZ after relapse occurring 18 months after a first TMZ cycle.

Background

Prolactinomas are the most common type of pituitary adenomas, accounting for about 40% of the total (1, 2). Endocrine symptoms are commonly related to hyperprolactinemia and hypogonadism. According to size, prolactinomas are classified as macro when the largest diameter is more than 10 mm at MRI. They are usually benign neoplasms but compression of adjacent anatomic structures may occur in large tumors, causing visual impairment and headache (1, 2).

First-line treatment is medication with dopamine-agonist drugs, mainly cabergoline (Cab), capable of normalizing PRL levels and restore eugonadism in most cases, as well as to shrink tumor, thus relieving local compression (1, 2). Approximately 11% of prolactinomas are resistant to treatment with Cab, despite maximal dose titration, and these tumors are typically treated with surgery (3). Radiotherapy is occasionally required.

In rare cases, prolactinomas may have or acquire an aggressive behavior, with uncontrolled tumor growth and PRL hypersecretion. These lesions can recur or reincrease despite multimodal therapy, including Cab, multiple surgical resections and radiation (1, 2, 3).

Here, we report the case of a man affected by macroprolactinoma that acquired an aggressive course after years on Cab, requiring multiple cycles of chemotherapy with temozolomide (TMZ).

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Case presentation

In 1997, a 63-year-old male was referred to the Endocrine Unit for right hemianopia with visual acuity impairment and a huge invasive tumor with both infra- and suprasellar extension (maximum diameter 25 mm). Hormonal evaluation showed pathologic hyperprolactinemia (PRL: 2300 µg/L, normal range (nr): 4–15 µg/L; 48 760 mIU/L, nr: 85–318 mIU/L) and panhypopituitarism: morning cortisol 66 nM/L (nr: 165–607), free thyroxine: 86 pM/L (nr: 90–230), total testosterone: 2.1 nM/L (nr: 9.7–38), IGF-1: 4 nM/L (nr: 4–32).

Cab treatment (2 mg/week) was started, as well as replacement therapy with corticosteroids, thyroxine, and, later on, testosterone. PRL levels significantly decreased (to 618, 81 and 34 µg/L – 13 102, 1717, 721 mIU/L – after 1, 3 and 12 months, respectively). Visual acuity progressively improved up to normalization and MRI showed a significant progressive shrinkage, with the complete disappearance of the suprasellar portion of the tumor and the appearance of a partial empty sella. In the following 3 years, PRL remained stable and MRI showed no change.

After 4 years, while still on Cab 2 mg/week, PRL increased up to 154 µg/L (3265 mIU/L) and MRI showed partial intrasellar regrowth of the adenoma. Notwithstanding Cab uptitration to 3.5 mg/week, PRL gradually raised (up to 500 µg/L, 10 600 mIU/L) without further increase in tumor volume. Transsphenoidal surgery was performed in 2003. Histopathological examination showed pituitary adenoma with positive immunostaining for PRL and Ki67 2%. After surgery, PRL was markedly lowered (to 33 µg/L, 700 mIU/L), but MRI showed the persistence of an intrasellar tumor. Cab was administered again (maximum dosage: 3.5 mg/week), but no change was observed in tumor volume. Two years after surgery, PRL was 200 µg/L (4240 mIU/L) and the patient underwent a second transsphenoidal unsuccessful tumor resection. Histopathological examination was superimposable to the former; PRL values remained high (310 µg/L, 6572 mIU/L), without any change in tumor size. The patient underwent fractionated radiotherapy in 2006 (total dose: 39.6 Gy).

After radiotherapy, PRL decreased (87 µg/L and 57 µg/L, – 1844 mIU/L and 1208 mIU/L – at 3 and 12 months, respectively) and a slight reduction of adenoma size was observed. In the next 4 years (on Cab 1.5 mg/week), both PRL values and tumor size remained stable.

In 2011, 4 years after radiotherapy, PRL reincreased (to 773 µg/L, 16 388 mIU/L) as tumor size, and the patient underwent a third neurosurgery (immunohistochemistry was positive for PRL, no mitosis were shown, Ki67 was 2%, MGMT evaluated by PCR was negative, i.e. the promoter was unmethylated). Neither PRL values were normalized (350 µg/L – 7420 mIU/L – immediately after surgery, and 564 µg/L – 11 957 mIU/L – 1 month later) nor MRI did show any change.

Six months later, PRL raised to 620 µg/L (13 144 mIU/L) but tumor volume remained stable without visual field alterations and clinical conditions of the patient remained excellent. Whole-body MRI did not show secondary lesions. Based on the worsening of disease in spite of three surgical resections by a skilled surgeon and one course of radiotherapy, chemotherapy with TMZ was added to the ongoing Cab treatment, using the schedule of 200 mg/m^2 for 5 days every 28 days, up to six cycles. After the 3rd cycle, both PRL values (256 µg/L, 5427 mIU/L) and tumor size decreased. The treatment was well tolerated and safety parameters remained normal. After 1 year, 6 months after TMZ discontinuation, further tumor shrinkage was observed and PRL dropped to 76 µg/L (1611 mIU/L).

PRL levels remained stable for 18 months following the end of TMZ, but eventually reincreased gradually up to 1219 µg/L (25 843 mIU/L), together with intrasellar increase of tumor size. A new TMZ course was started with the same schedule for 12 months. PRL values dropped again to 480 µg/L (10 176 mIU/L), 640 µg/L (13 568 mIU/L), 525 µg/L (11 130 mIU/L), 500 µg/L (10 600 mIU/L), 487 µg/L (10 324 mIU/L), and 553 µg/L (11 723 mIU/L) after 1, 2, 3, 4, 6 and 12 months from TMZ start, respectively, with a slight reduction of tumor size. No side effects developed. After the completion of the second TMZ cycle PRL levels were 525 µg/L (11 130 mIU/L), 646 µg/L (13 695 mIU/L), 629 µg/L (13 335 mIU/L) and 1088 µg/L (36 400 mIU/L), at 6, 9, 12 and 18 months, respectively. The patient is still in good clinical conditions and tumor size is not increased (Fig. 1).

Discussion

Our patient was affected by a macroprolactinoma that acquired resistance to treatment and an aggressive behavior after partially successful prolonged treatment with Cab (persistence of high PRL levels and tumor tissue). He required then multimodal treatment, with repeated surgery, and fractionated radiotherapy, and eventually chemotherapy with TMZ.

Pituitary adenomas are usually benign lesions, but mainly macroprolactinomas can occasionally acquire

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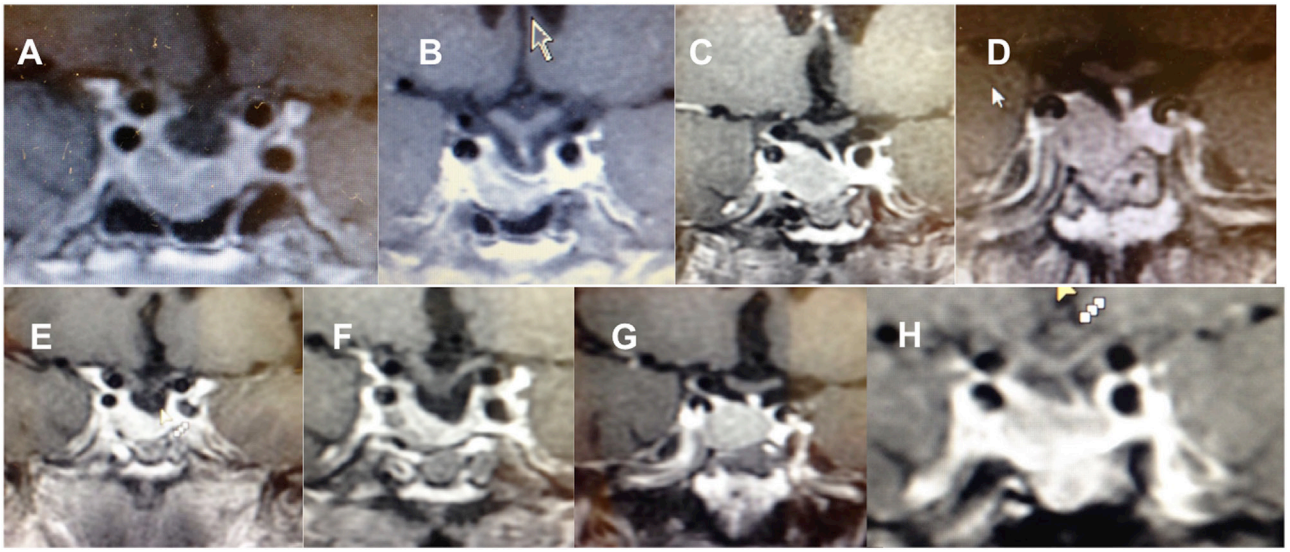

Figure 1
Serial images. (A) Before the first neurosurgery. (B) After the first neurosurgery. (C) After the third neurosurgery. (D) Four years after irradiation. (E) At 3 months during the first TMZ cycle. (F) At 6 months after the withdrawal of the first TMZ cycle. (G) At 18 months after the withdrawal of the first TMZ cycle. (H) At 6 months during the second TMZ cycle.

an aggressive behavior, thus representing a tremendous challenge for the endocrinologist. The European Society of Endocrinology (ESE) has just issued guidelines for the management of aggressive pituitary tumors and carcinomas (4). A prolactinoma is defined as resistant to treatment if PRL normalization and tumor shrinkage are not achieved in spite of appropriate dose titration (1, 2, 3). A tumor is defined aggressive whenever it is radiologically invasive with unusually rapid growth rate or when clinically relevant tumor growth occurs despite optimal standard therapies (surgery, radiotherapy and conventional pharmacological treatments) (4). Only the presence of distant metastases defines pituitary carcinoma.

TMZ is a peroral alkylating drug that was approved initially for the treatment of glioblastoma, and eventually was demonstrated to be effective in aggressive pituitary tumors and carcinomas (5). An endogenous DNA repair protein, O(6)-methylguanine methyltransferase (MGMT), can remove the methyl group and thereby potentially counteract the cytotoxic effect of TMZ.

A few cases of TMZ treatment in prolactinomas were described, most successful as this case. It was previously described that MGMT immunostaining in the tumor was predictive of treatment failure (6, 7). However, the multicentric French study showed that this was not the rule, and anyway it is worthwhile a three-cycle challenge to test individual TMZ sensitivity (8). Unfortunately, the determination of MGMT in our patient was not performed directly by immunohistochemistry but only indirectly by PCR evaluation of the methylation status of the promoter.

Almost all cases described in literature point to TMZ effectiveness in the treatment of resistant prolactinomas. A systematic review describing 23 aggressive prolactinomas and 19 PRL-secreting carcinomas showed TMZ efficacy in 75% as evaluated by PRL levels (8.3% normalization and 8.3% progression) and in 76.5% as evaluated by tumor volume (1/34 complete response and 20.6% progression) (9). These figures were superimposable to those reported by McCormack *et al.* (7). Even overall survival was improved by TMZ in a series of 43 patients (13 prolactinomas) (10).

TMZ is usually well tolerated (7). Whereas nausea and vomiting are generally well controlled with anti-emetics, bone marrow suppression prompted TMZ withdrawal in 11% of patients in the retrospective observational survey by ESE (7). The rechallenge with TMZ monotherapy was rarely reported in patients with disease recurrence after a first successful TMZ cycle, and it was unsuccessful in most cases (7). This case is thus an exception.

Many issues are still unresolved. Concerning molecular pattern, it is not yet established the role of MGMT, the strongest prognostic factor and powerful predictor of response to TMZ chemotherapy in patients with glioblastoma. It was described a strong association (OR=9.35; P=0.0030) between MGMT-negative staining

and sensitivity to TMZ in 15 out of 20 prolactinomas (5). Whether additional molecular markers other than MGMT expression may predict treatment response is still unknown. However, both the drop of endocrine tumor marker (such as ACTH or PRL in hypersecreting tumors) and tumor volume at 3 months may prove useful tools for assessing the response to TMZ, limiting its use if not effective (5). Moreover, it should be investigated whether alternative regimens that increase the duration of exposure and the cumulative dose of TMZ, as employed for high-grade gliomas, might be more effective even for prolactinomas. Generally, only standard TMZ schedule (150–200 mg/m^2 for 5 days every 28 days) has been investigated, but the 21-day continuous schedule at a lower daily dose (85–125 mg/m^2) or a continuous metronomic schedule of 50 mg/m^2/day (11) might be tested to verify the potential effect on tumor as well as the best balance between efficacy and safety.

Also timing of chemotherapy should be clarified. To date, clinical guidelines by Endocrine Society (2), Pituitary Society (1) and ESE (4) recommend the use of TMZ only as a third line after standard medical treatment (with dopamine-agonist drugs) and neurosurgery/radiotherapy. In the light of more and more cases in the literature with a good response to TMZ, it will be important to consider TMZ as a second-line treatment, prior or together with RT in order to avoid neurotoxicities especially in young patients.

It is unclear whether and when TMZ can be safely discontinued after the achievement of tumor growth control. Likewise, it is uncertain the effect of stopping and restarting treatment, and it has not yet been explored the opportunity to prolong the treatment indefinitely in case of disease relapse after a first cycle of treatment.

Hence, it is necessary to standardize the use of TMZ, identifying specific molecular patterns that could predict clinical course and response to therapy. We still need to identify appropriately selected population where TMZ can be highly effective, in order to obtain individual tailoring of care. Large randomized controlled trials would be useful to evaluate the role of TMZ in patients affected by aggressive refractory pituitary adenomas, and the possible combination of TMZ with other cytotoxic drugs, but we are aware that it will be extremely difficult to collect such kind of data.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Written informed consent has been obtained from the patient for publication of the submitted article.

Author contribution statement
B Z and R C were the endocrinologists involved in the care of the patient. G S and A S were the neurooncologists responsible for TMZ administration. R A wrote the paper.

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