Long-term control of a MEN1 prolactin secreting pituitary carcinoma after temozolomide treatment

Carcinome hypophysaire et néoplasie endocrinienne multiple de type 1 : efficacité à long-terme du temozolomide

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Abstract

We report here a rare case of a young male patient presenting with a Multiple Endocrine Neoplasia Type 1 - prolactin-secreting pituitary carcinoma, controlled long-term after temozolomide withdrawal. Initial presentation was pituitary apoplexy leading to surgery. Dopamine agonists and radiotherapy allowed control of prolactin secretion and pituitary remnant. Metastasis appeared 10 years after initial presentation, leading to the diagnosis of pituitary carcinoma. At that time, dopamine agonists were no more effective; temozolomide, an oral alkylating agent, was administered for 24 cycles, and allowed decrease of the volume of the pituitary lesion and metastases. The patient is still currently followed in our department, 3 years after temozolomide withdrawal: prolactin level and pituitary tumor volume remain controlled without any chemotherapy. To our knowledge, this is the first case of MEN1 prolactin secreting pituitary carcinoma controlled long-term after temozolomide discontinuation.

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Résumé

Nous rapportons le cas d’un patient porteur de Néoplasie endocrinienne multiple de Type 1, ayant présenté un carcinome hypophysaire à prolactine contrôlé après arrêt prolongé de temozolomide. Le patient a initialement présenté une apoplexie hypophysaire pour laquelle il a bénéficié d’une chirurgie d’exérèse partielle, puis d’une radiothérapie, et de fortes doses de dopaminergiques. Il a présenté des métastases dix ans après le diagnostic de carcinome, alors que les taux de prolactine n’étaient plus contrôlés par dopaminergiques. Un traitement par temozolomide, un agent alkylant, a été délivré pendant 24 cycles. Ce traitement a permis une diminution du volume des lésions secondaires et du résidu tumoral. Le patient est actuellement toujours suivi dans notre service, trois ans après l’arrêt du temozolomide : les taux de prolactine, et les volumes des lésions sont désormais stabilisés sans traitement.

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1. Introduction

Pituitary carcinomas are rare tumors (0.1% of all pituitary tumors) defined by craniospinal or systemic metastatic spread [1–3]. Diagnosis of malignancy is usually delayed by several years as these tumors initially behave as benign pituitary adenomas. Prognosis is poor: at the time of diagnosis, mean time to survival is close to 4 years [1]. Multimodal management with surgery, antisecretory drugs and radiotherapy, is usually ineffective [1,4]. Chemotherapy was not effective until recently. In the last 2 years, several case reports of pituitary carcinomas showed short-term antisecretory and antitumor efficacy of temozolomide [5–9], an oral alkylating agent classically used in the management of glioblastoma [10]. Recent studies based on
larger cohorts of patients reported immediate anti tumor and antisercreatory responses in 35 to 75% cases [11,12]; some studies, but not all, identified the level of expression of the enzyme MGMT as a possible predictor of drug efficacy [11–14]. However, the main drawback of all these studies was the lack of mid to long-term follow-up data, precluding any firm conclusion on the final prognosis after temozolomide withdrawal.

We report here the case of a male patient with a prolactin-secreting pituitary carcinoma treated by temozolomide after failure of classical antisercreatory and antitumor therapies. Interestingly, this carcinoma was part of Multiple Endocrine Neoplasia Type 1 (MEN1). Although MEN1 is known to be associated with locally invasive and recurrent pituitary adenomas [15,16], only one case report described the occurrence of a TSH secreting pituitary carcinoma in this condition [17]. Our patient, who is still currently followed in our Department 3 years after withdrawal of temozolomide, is the first reported prolactin-secreting pituitary carcinoma in a patient with MEN1 to show a prolonged response after withdrawal of this chemotherapy.

2. Clinical case

Patient FG presented sudden oculomotor paresis and signs suggestive of meningitis at the age of 31 in 1995. Lumbar puncture did not find any germs. Brain CT scan showed a hemorrhagic pituitary tumor, with supra- and latero-sellar extensions (Fig. 1). Ophthalmological evaluation was normal, and did not show any visual field defect. The patient was treated by transsphenoidal surgery, but resection was incomplete. Pathology was in favor of a necrotic pituitary tumor, without any specific secretory characteristics. Presurgical hormonal samples, mitotic indexes and MGMT status were not available. Immediate postsurgical prolactin was 192 ng/ml in favor of a macroadenoma. Bromocriptine was initiated at the dose of 5 mg/day. Hormonal replacement was also begun, as the patient presented panhyopituitarism, while whole body 18F-FDG PET/CT frontal image showed complete disappearance of the pituitary, spinal, 4th ventricle and bone hypermetabolic areas. Of note, from 1997 to 2011, pancreatic lesions remained unchanged. The patient presented no recurrence of hyperparathyroidism.

The patient had been suffering from symptomatic urinary lithiasis since 1994, and was diagnosed with primary hyperparathyroidism. Blood samples showed hypercalcemia (2.82 mmol/l, N: 2.25–2.55) and increased parathormon levels (58 pg/ml, N: 15–45). Two hyperplasic parathyroid glands were removed surgically. Diagnosis of MEN1 was confirmed by menin gene sequencing: the patient was carrying a previously unreported heterozygous false sense mutation on exon 3 (p. C165R), and three previously reported polymorphisms. We tried to determine whether other family members were carrying the mutation: DNA samplings were unavailable for the parents; two brothers and one sister, who had no personal history of endocrine tumor, were not carrying the mutation. Finally, pancreatic CT was performed in the patient: three centimetric cystic tumors were observed; normal values of pancreatic peptides were in favor of non-secreting tumors.

In 1998, prolactin rose up to 2800 ng/ml despite maximal doses of bromocriptine. Pituitary MRI revealed an intrasellar tumor with latero-sellar extension. Pituitary fractionated stereotactic radiotherapy was performed (maximal dose, 46 Gy), and bromocriptin was maintained. Three months after radiotherapy, intrasellar remnant largest diameter was 10 mm. Prolactin level was 558 ng/ml.

Prolactin levels decreased and plateaued between 100 and 200 ng/ml. In 2005, prolactin level increased rapidly up to 1140 ng/ml. Bromocriptine was replaced by quinagolide, and then cabergoline (4.5 mg/week), without further efficacy. In the beginning of 2006, the patient presented severe headache with oculomotor paresis. MRI showed a large heterogeneous hemmorhagic pituitary tumor (37.8 cm³) (Fig. 2), and a secondary localization in the fourth ventricle. Lumbar puncture found carcinoma cells dissemination in cerebro-spinal fluid. Interestingly, prolactin immuno-staining was positive, confirming the diagnosis of prolactin-secreting carcinoma. Prolactin level rose to 11800 ng/ml. Spinal MRI displayed several vertebral metastases (C1, C4, C5, C6, T1, S1, S2). 18FDG PETScan showed hyperactive pituitary, cerebral, and spinal lesions, in favor of metastatic localizations of a prolactin secreting pituitary carcinoma. At that time, the patient received replacement therapy for panhypopituitarism, and had no diabetes insipidus.

Because of the lack of efficacy of dopamine agonists and radiotherapy, and the presence of metastases making surgical cure impossible, the patient was treated with temozolomide. Temozolomide was initiated at the dose of 150 mg/m², and then, 200 mg/m², 5 days a week, every 4 weeks. Cabergoline was withdrawn. Temozolomide was given from October 2006 to October 2008, for a total of 24 sessions. After the second session, there was no more detectable malignant cell in cerebro-spinal fluid; prolactin level was 6950 ng/ml. After the ninth session, MRI showed decreased volume of the pituitary (27 cm³) and the fourth ventricle lesions (0.27 cm³). After the 13th session, there was no more visualized mass close to the fourth ventricle. Prolactin level was 470 ng/ml. After the 20th session, 18FDG PetScan did not find any residual hyperactive signal in the pituitary and the vertebrae. After the last session, prolactin level was 254 ng/ml. Pituitary and vertebral MRI showed decreased volume of pituitary remnant (by 62%) and vertebral metastases, in comparison with pretemozolomide MRI.

The most recent follow-up evaluation was performed 3 years after temozolomide withdrawal. The patient had no complaint. Prolactin level was 98 ng/ml without cabergoline. Last MRI found stable intrasellar remnant (Fig. 3) and vertebral lesions, while whole body 18F-FDG PET/CT frontal image showed complete disappearance of the pituitary, spinal, 4th ventricle and bone hypermetabolic areas. Of note, from 1997 to 2011, pancreatic lesions remained unchanged. The patient presented no recurrence of hyperparathyroidism.

3. Discussion

Pituitary carcinomas are usually difficult to diagnose, with a latency period estimated between 7 to 10 years [1]. Our patient presented with extrapituitary metastases 11 years after initial diagnosis of pituitary adenoma. Several signs might have been suggestive of a more aggressive pituitary tumor: early recurrence, 2 years after surgery; partial antisercreatory efficacy
Fig. 1. 1995 - Coronal (a) and sagittal (b) T1-weighted pituitary MRI, after surgery: postoperative sequellae without any large visible residual adenomatous tissue.

Fig. 2. 2006 - Cerebral 18F-FDG PET/CT fusion image (c) and axial image: pituitary, fourth ventricle, spinal, and cervical, thoracic, sacral vertebrae (C1, C4, C5, C6, T1, S1, S2) hypermetabolic areas. Coronal (e), sagittal (f), axial (g) T1-weighted MRE: large adenomatous residue in the left cavernous sinus of 37.8 cm³, with necrotic and hemorrhagic changes. Pituitary residue apoplexy.
of dopamine agonists; tumor growth despite dopamine agonists. However, none of these criteria allows distinction between an aggressive pituitary adenoma, and a pituitary carcinoma. MEN1 is usually associated with more aggressive pituitary tumors [16], but, to our knowledge, only one case of MEN1 with a pituitary carcinoma has been reported to date [17]. Molecular mechanisms leading to pituitary carcinomas remain largely unknown to date. Interestingly, although undetectable menin expression has been reported in pituitary carcinomas biopsies [18], and menin is a tumor suppressor gene, MEN1 pituitary carcinomas remain an exceptional occurrence.

Our patient was treated with surgery first because of its presentation as pituitary apoplexy. The therapeutic sequence then included dopamine agonists, and radiotherapy because of tumor growth. Unexpectedly, tumor kept on growing rapidly despite radiotherapy. Regrowth of a pituitary adenoma after radiotherapy is highly unusual. Antitumor efficacy is close to 90-100% cases in the series reported to date in the literature for non-secreting pituitary adenomas [19]. This antitumor effect is usually observed during the first year after the procedure. Our case clearly indicates that the lack of antitumor efficacy of radiotherapy should be an indicator for clinicians to look for a pituitary carcinoma.

Series reported in the literature about the treatment of pituitary carcinomas show that classical therapeutic modalities are usually ineffective long-term. Temozolomide, an alkylating oral agent, is a promising chemotherapy in this setting. Since 2006, 44 patients have been reported as treated by temozolomide for an aggressive pituitary tumor, including 19 with a pituitary carcinoma [5–9,11,12]. Short-term antisecretory efficacy and tumor control was reported in about 50–60% cases. These results are however biased by the lack of mid to long-term follow-up data after temozolomide withdrawal. Our patient was presenting severe clinical signs with diffuse metastatic spread, which made him a good candidate for temozolomide, as this drug is able to cross the blood-brain barrier. Interestingly, temozolomide induced a rapid and dramatic decrease of prolactin level and tumor volumes both in primary and secondary lesions. Our patient is currently still being followed in our Department 3 years after temozolomide withdrawal: at last follow-up, prolactin level

Fig. 3. 2011 - Whole body $^{18}$F-FDG PET/CT frontal image (a): complete disappearance of the pituitary, spinal, 4th ventricle and bone hypermetabolic areas. Coronal (b) and sagittal (c) T1-weighted MRI.
was stable, and pituitary and vertebral lesions were unchanged compared to immediate post-temozolomide evaluation. Of note, our patient was also treated by radiotherapy, and the long-term control of the disease may also at least be partly due to the delayed efficacy of this procedure.

In conclusion, this is to our knowledge the first case of MEN1 prolactin secreting pituitary carcinoma treated with temozolomide and controlled long term after withdrawal of the drug. A combined treatment with temozolomide to control acute signs, and radiotherapy to obtain long-term control, might be of major interest in patients with pituitary carcinomas. Our case also shows that several indicators, growth of pituitary tumor despite radiotherapy most importantly, might suggest the need for a closer follow-up in a search for metastatic lesions that are the hallmark of a pituitary carcinoma.

Disclosure of interest
The authors declare that they have no conflict of interest concerning this article.

References