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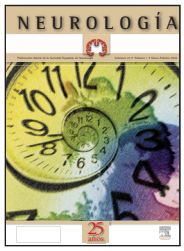

ORIGINAL ARTICLE

Use of Bevacizumab for neurological complications during initial treatment of malignant gliomas

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KEYWORDS
High grade glioma;
Radiation necrosis;
Tumour progression;
Oedema;
Corticosteroids;
Bevacizumab

Abstract
Introduction: High grade gliomas are the most common primary malignant brain tumours. Treatment with chemoradiation and adjuvant chemotherapy with Temozolomide may prolong survival but some patients develop complications during or soon after therapy due to radiation necrosis, oedema or tumour progression.
Patients: We report the use of Bevacizumab in four patients with newly diagnosed high grade gliomas who developed cerebral oedema due to tumour progression or radiation necrosis that did not respond to corticosteroids, and who were not candidates for surgical debulking.
Outcomes: All four patients had a rapid response to treatment with bevacizumab, tolerating a decrease of the dose of corticosteroids, and were able to continue their standard therapy.
Conclusions: Bevacizumab is effective in controlling some of the neurological complications from oedema, radiation necrosis, or rapid tumour progression during the initial treatment of malignant gliomas.

PALABRAS CLAVE
Glioma de alto grado;
Radionecrosis;
Progresión tumoral;
Edema;

Utilización de bevacizumab en las complicaciones neurológicas durante el tratamiento inicial de los gliomas malignos

Resumen
Introducción: Los gliomas de alto grado son los tumores malignos más frecuentes del sistema nervioso central. El tratamiento con quimiorradioterapia y quimioterapia adyu-

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Corticoides;
Bevacizumab

vante con temozolomida puede prolongar la supervivencia, pero algunos pacientes desarrollan complicaciones durante o poco después de acabar el tratamiento debido a radionecrosis, edema o progresión tumoral.
Pacientes y métodos: Presentamos el uso de bevacizumab en 4 pacientes que desarrollaron edema cerebral en relación con radionecrosis o progresión tumoral durante la fase inicial del tratamiento, con respuesta inadecuada a los corticoides y que no eran subsidiarios de tratamiento quirúrgico por la localización de la lesión o la mala situación clínica.
Resultados: Los cuatro pacientes presentaron una rápida respuesta al tratamiento con bevacizumab, lo cual permitió reducir la dosis de corticoides y continuar el tratamiento estándar.
Conclusiones: Bevacizumab es efectivo en el control de algunas complicaciones neurológicas debidas a edema, radionecrosis o rápida progresión de tumores no extirpables durante el tratamiento inicial de los gliomas malignos.

Introduction

High grade gliomas, including multiform glioblastoma (MGB) and anaplastic astrocytoma (AA), are the most frequent primary cerebral tumours. Mean survival varies with the histological grade: 14 months for MGB and 36 months for AA. Treatment of AA consists in surgery and radiation therapy whereas for MGB, surgery, chemoradiation therapy (temozolomide [TMZ] associated with external radiation therapy on the surgical bed) and 6 cycles of adjuvant chemotherapy with TMZ.[1] The treatments are generally well tolerated, which has contributed to an improvement in patients' quality of life. In some clinical situations, however, as in cases of extensive tumours in which it has not been possible to perform ample resection, or due to the development of radionecrosis during treatment, patients may present clinical deterioration that does not always respond to corticosteroids or that obliges the use of high doses causing intolerable side effects, all of which prevents the continuation of standard anti-tumour treatment. In such situations, the use of bevacizumab, a monoclonal antibody targeting the vascular endothelial growth factor (VEGF) that normalizes vascular patency[2,3] may be of therapeutic benefit. Furthermore, in 2009, the Food and Drug Administration (FDA) accelerated the approval process of this drug for the treatment of recurrent MGBs due to the good results in phase II studies.[4-6]

We report here on 4 patients with high-grade gliomas in which the clinical complications, including oedema, radionecrosis or tumour progression, prevented the continuation of the standard treatment. The use of bevacizumab quickly improved the patients' condition and allowed them to finish treatment.

Patients

Case 1

Male, 44 years old, diagnosed in September, 2009, as having left temporal AA after presenting several partial epileptic seizures. Sub-total extirpation was performed due to the location of the tumour. Following surgery, he presented right hemicorporal weakness and discreet aphasia. Six weeks after the surgical procedure, while he was in the first week of chemoradiation therapy, the patient presented deterioration in strength and language in connection with the oedema caused by the treatment, as well as tumour progression, neither of which improved with increased doses of corticosteroids (8 mg of dexametasone/day) (fig. 1). It was decided to start treatment with bevacizumab, which stabilized his clinical condition and allowed his corticosteroid to be clinical trial to one half of the dose, thus enabling him to finish the chemoradiation therapy with minimal morbidity (fig. 1).

Case 2

Male, 39 years old, diagnosed in January, 2009, as having right fronto-parietal MGB after several episodes of partial seizures. Total extirpation of the tumour was performed and 4 weeks after the procedure he started treatment with radiation therapy. Chemotherapy was delayed by two weeks due to problems with his insurance. Four weeks after starting with radiation, the patient presented repeated epileptic seizures and, after a magnetic resonance image (MRI) showed it was a recurrence of the tumour, he received additional surgery. He subsequently had to be re-admitted due to an abscess in the surgical area for debriding and antibiotic treatment, so the chemoradiation therapy was suspended for a few weeks. Treatment was begun again with radiation therapy while he was receiving antibiotic treatment and the start of the chemotherapy was delayed until his antibiotic treatment was completed. On conclusion of the antibiotic treatment and radiation therapy, the patient presented mild left hemiparesis and an intact cognitive situation. Two weeks after finishing radiation therapy and before starting the 6 cycles of TMZ, while still under treatment with 24 mg of dexametasone per day, he was admitted for motor impairment and signs of mental confusion. An imaging test revealed a major cerebral oedema (fig. 2) and, since he had not responded to corticosteroid treatment, it was decided to use bevacizumab. A considerable improvement was observed within 48 hours and he could be discharged in 5 days (fig. 2). The week after the first dose of bevacizumab, the patient was able to attend the clinic visit by walking independently.

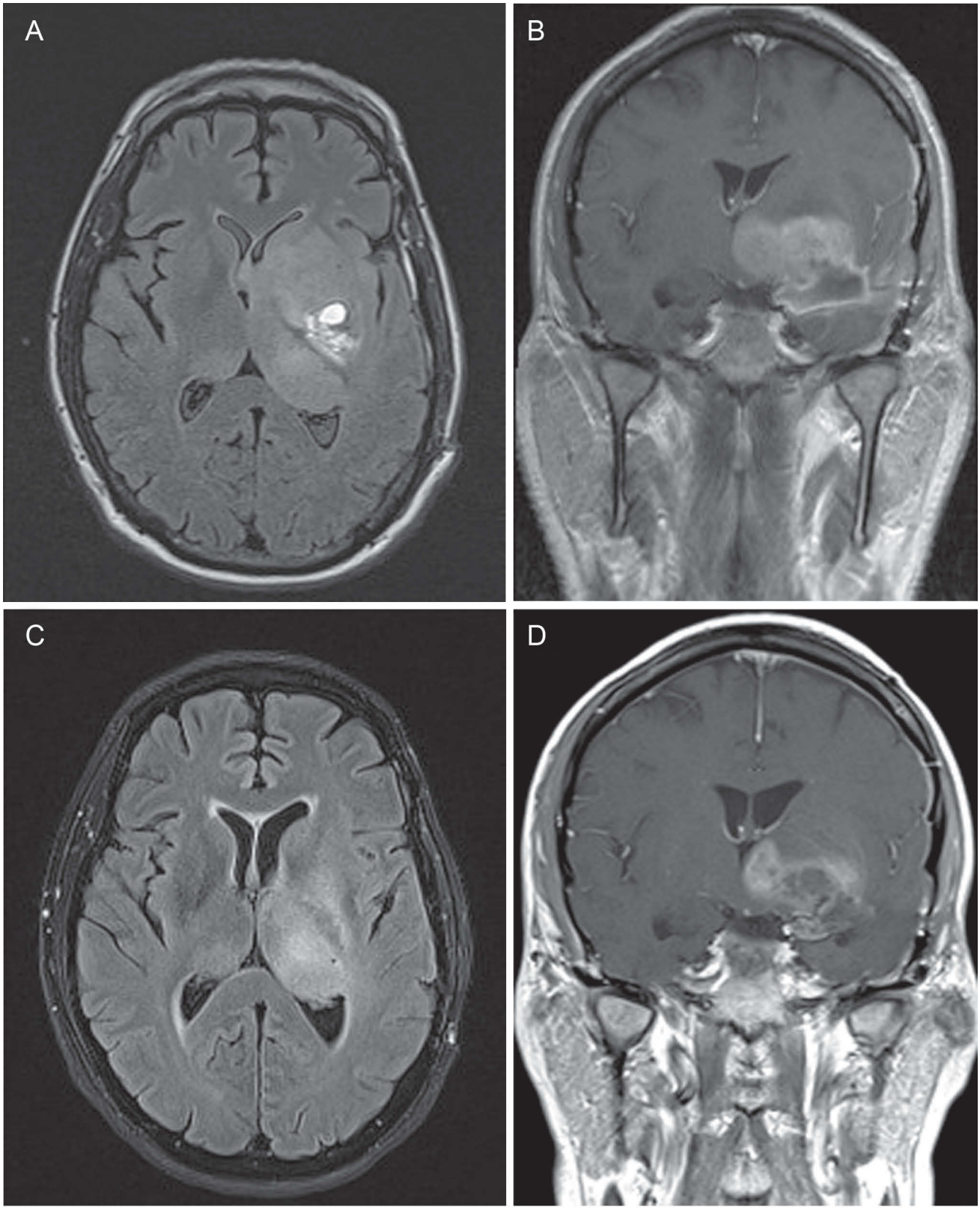

Figure 1 Magnetic resonance images of patient 1. Images A and B correspond to FLAIR and T1 gadolinium-enhanced sequences in the phase when his symptoms worsened. Images C and D correspond to the same sequences after treatment with bevacizumab (one cycle). Note the reduction in the mass effect, as well as the size of contrast uptake in the tumour. Furthermore, it is possible to observe a re-expansion of the ventricles to normal size.

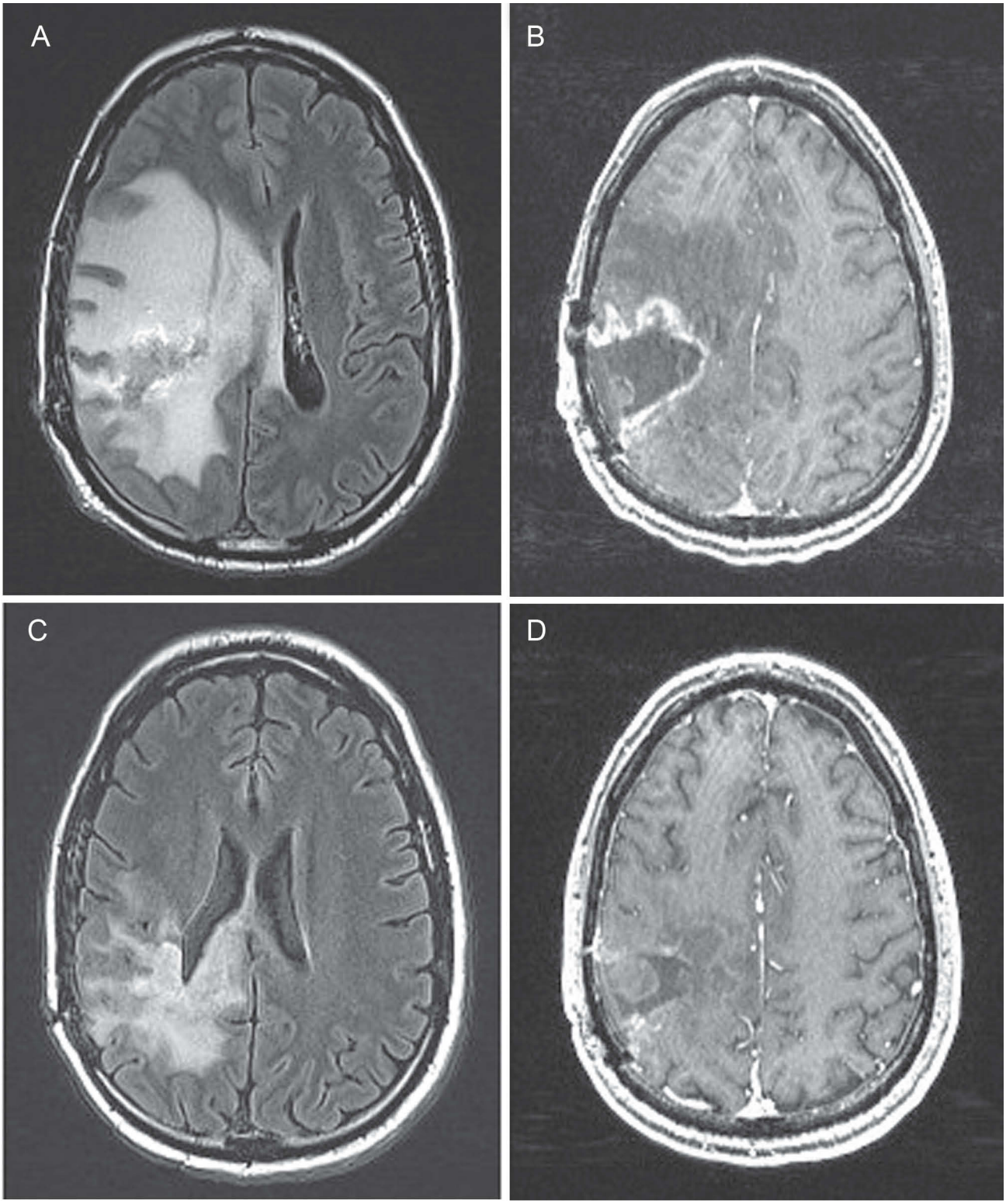

Figure 2 Magnetic resonance images of patient 2. Images A and B correspond to FLAIR and T1 gadolinium-enhanced sequences obtained after the patient presented repeated epileptic seizures while in the fourth week of radiation therapy. Images C and D correspond to the same sequences after treatment with bevacizumab. In these images, it is possible to see a considerable reduction in the vasogenic oedema and resolution of the midline displacement. Furthermore, in the gadolinium-enhanced sequence, it is possible to observe the reduction in the size of contrast uptake in the tumour in comparison with its size prior to bevacizumab.

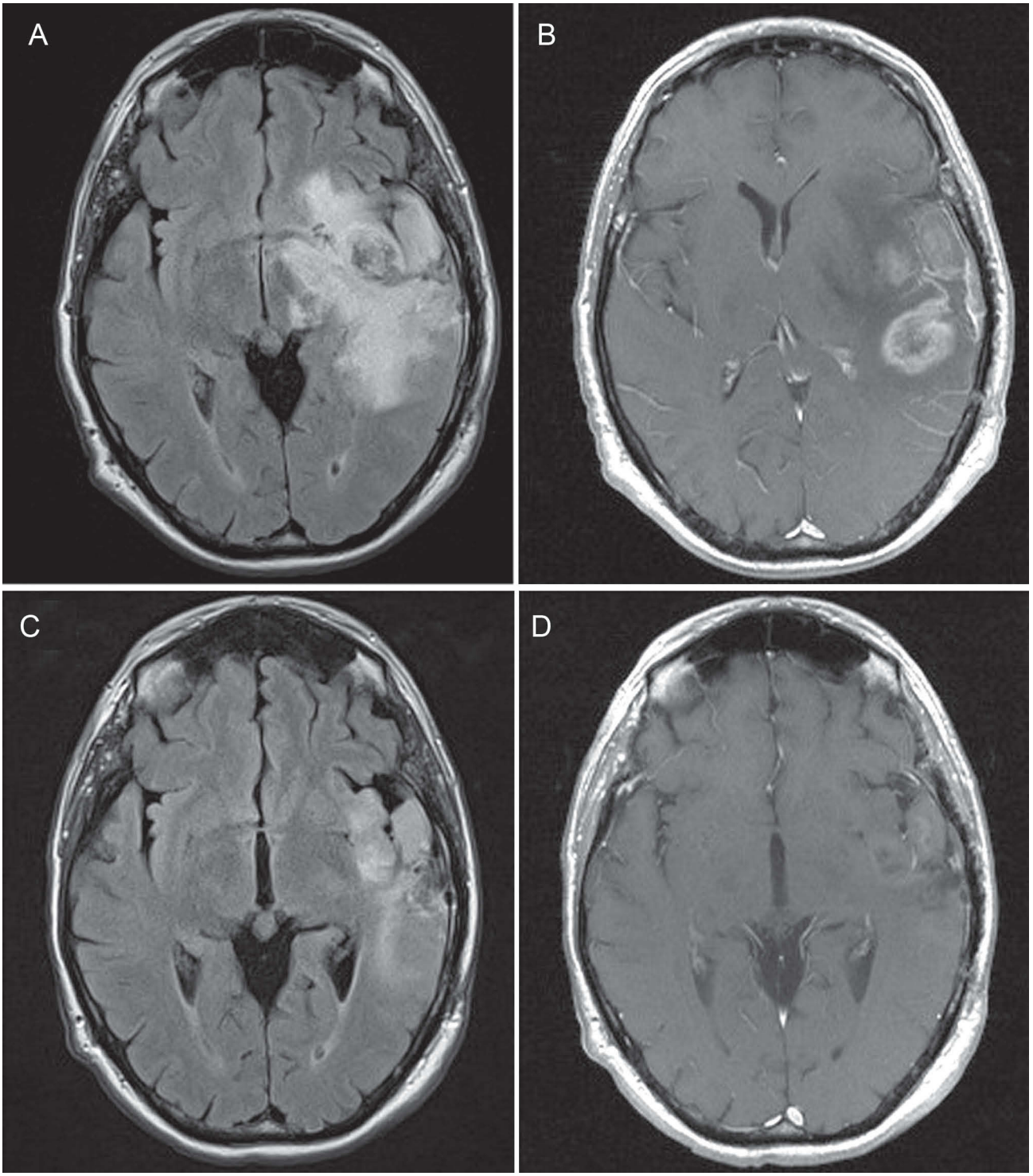

Figure 3 Magnetic resonance images of patient 3. Images A and B correspond to FLAIR and T1 sequences obtained three weeks after the patient completed treatment with chemoradiation therapy and after presenting a worsening of language skills. Images C and D correspond to the same sequences after two cycles of bevacizumab. It is possible to observe a considerable reduction in the vasogenic oedema, the mass effect and a reduction in the size of contrast uptake in the tumour.

Case 3

Male, 63 years old, diagnosed in July, 2009, as having left temporal AA after presenting several generalized seizure. Sub-total extirpation of the tumour was performed with the patient awake and using language mapping. Following the procedure, the patient had slight expression aphasia. Six weeks after the surgery, the patient started to receive chemoradiation therapy and continued with corticosteroid treatment until a few days after starting with radiation

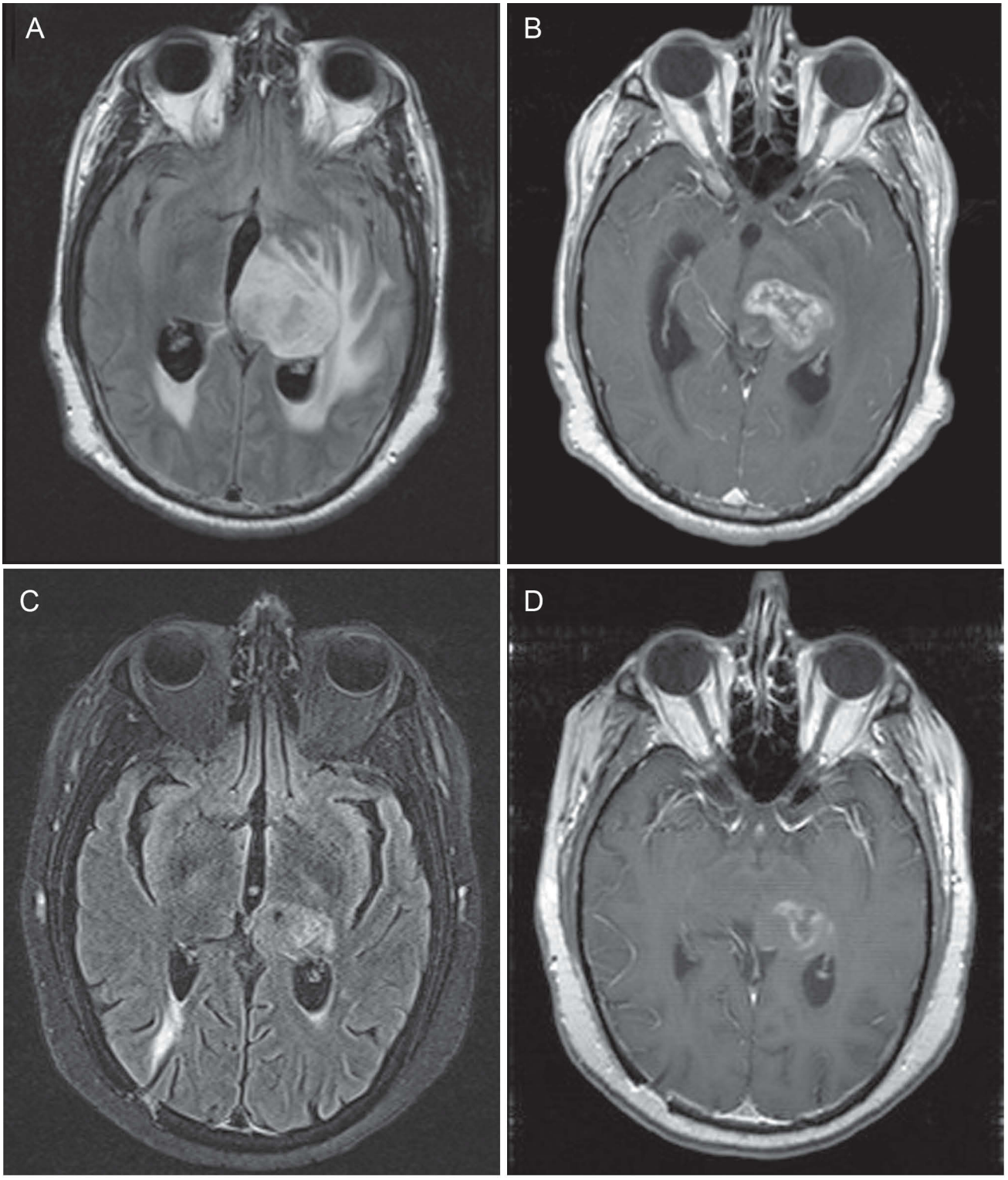

Figure 4 Magnetic resonance images of patient 4. Images A and B correspond to FLAIR and T1 sequences obtained after the patient developed a situation of major cognitive impairment on conclusion of the treatment with chemoradiation therapy. Images C and D correspond to the same sequences after one cycle of bevacizumab, and it is possible to see the almost complete resolution of the surrounding oedema.

therapy. Ten days after completing the 6 weeks of chemoradiation therapy, the patient debuted with major language difficulties and so treatment with dexametasone (4 mg per day) was re-started. This was associated with a partial but very transient improvement and a further MRI showed major oedema and tumour progression (fig. 3). At this time, it was decided to use bevacizumab to reduce the oedema and improve his neurocognitive situation, with the idea of re-starting adjuvant treatment with TMZ subsequently. His language improved notably in 48 hours and, after three cycles of Bevacizumab, the patient has re-started treatment with adjuvant TMZ (fig. 3).

Case 4

Male, 39 years old, presenting cephalea and right hemihypoesthesia deficit in September, 2009. MRI revealed a mass in the left thalamus and the biopsy confirmed that it was an MGB. Three weeks after finishing chemoradiation therapy, the patient developed nausea, cephalea and cognitive impairment that partially improved with low doses of corticosteroids. One day later, a further MRI showed tumour progression with extension into the brainstem and hydrocephaly (fig. 4). A ventriculoperitoneal shunt was performed with clinical improvement and, three weeks later, treatment was started with bevacizumab. Stabilization of his clinical condition was achieved after two treatment cycles (fig. 4), which allowed him to start the standard therapy cycles with TMZ without the need for additional treatment with bevacizumab.

Discussion

All four patients reported had high-grade gliomas and developed clinical worsening during or after treatment with chemoradiation therapy, thus preventing them for completing the standard course of treatment. Cerebral oedema may be secondary to tumour progression/ recurrence or to radionecrosis (also known as pseudoprogression) during or after chemoradiation therapy. In general, such an oedema can be controlled with corticosteroids and it is occasionally necessary to apply surgery to reduce the bulk of the tumour and the mass effect on neighbouring structures.

In the cases presented here, surgery was not considered due to poor clinical situation (case 2) or the location of the lesion (cases 1, 3 and 4), and the patients did not improve with increased doses of corticosteroids. In addition, in case 2, the increase in corticosteroids produced a situation of agitation and psychosis.

High-grade gliomas express high levels of VEGF, a powerful activator of angiogenesis and vascular patency. Bevacizumab is a monoclonal antibody that inhibits VEGF, thus normalizing vascular patency and reducing the oedema.[2,3] Its effects are speedy and can be noticed after only a single treatment dose. The reduction in intracranial pressure favours an improvement in the essential neurological functions in order to continue with treatment. Apart from improving the symptoms, bevacizumab allows a reduction in the dose of corticosteroids, thus avoiding its side effects.[3]

Bevacizumab has been approved for the treatment of metastatic colorectal cancer,[7] non-small-cell lung cancer,[8] HER2 negative breast cancer[9] and renal cancer[10] in combination with other courses of chemotherapy. In general, bevacizumab is a well-tolerated drug, but it is necessary to bear in mind its possible adverse effects. These include arterial hypertension and discreet haemorrhage, as well as less frequent complications such as thromboembolic events, scarring problems, proteinuria, intestinal perforation and reversible posterior encephalopathy. The patient described in case 1 developed an episode of deep vein thrombosis, and it is not possible to rule out that this might be an event related with the hypercoagulability typical of tumours.

Bevacizumab must be considered not only as second-line treatment for high-grade gliomas, but as a therapeutic possibility in patients who have developed progression of tumours that are not candidates for extirpation, radionecrosis, oedema associated with these complications, or who require high doses of corticosteroids in order to continue or complete standard anti-tumour treatment.

Conflict of interest

The authors declare no conflict of interest.

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