Pseudoprogression and Pseudoresponse: Imaging Challenges in the Assessment of Post Treatment Glioma

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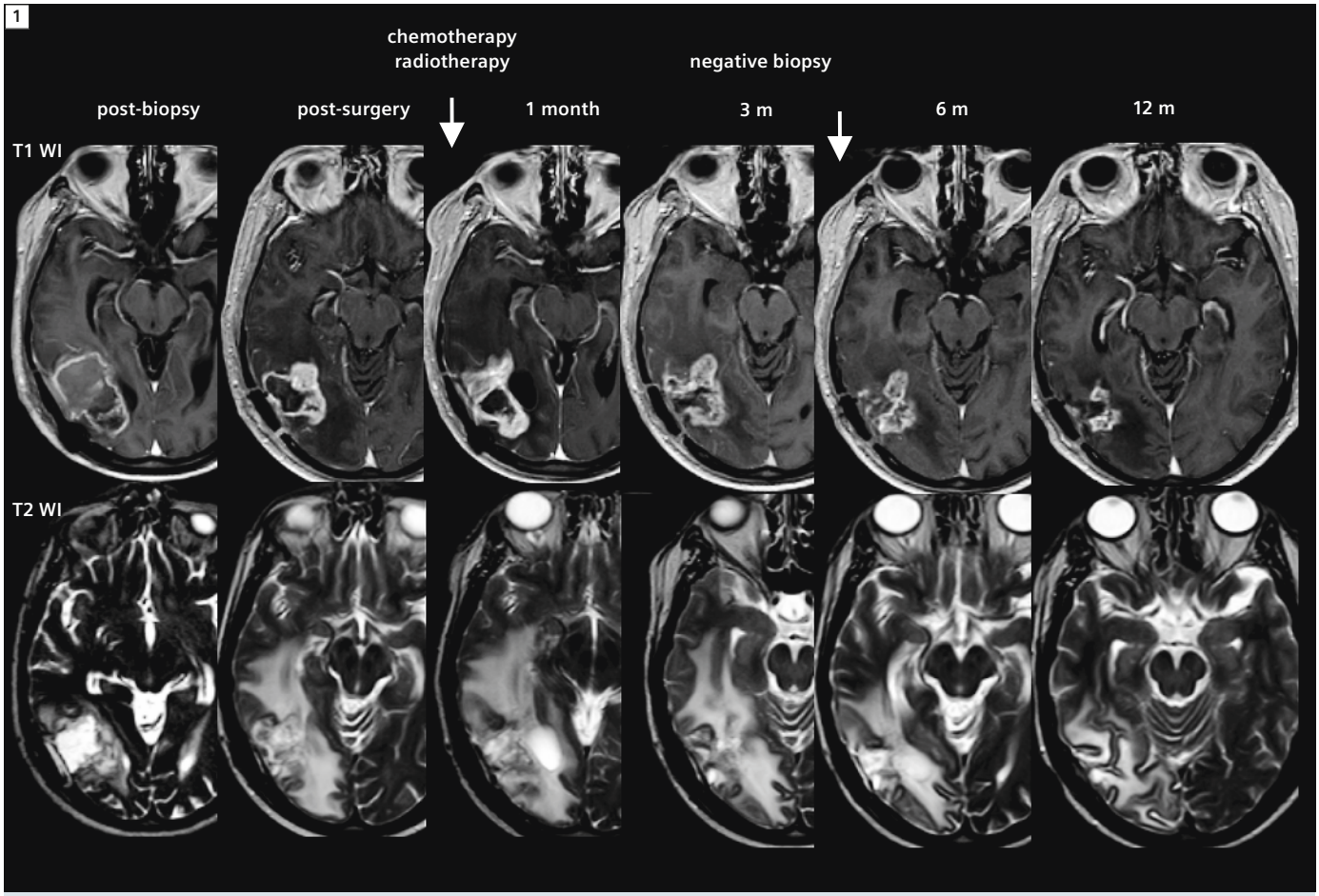
Gliobastoma multiforme is the most common primary malignant type of brain neoplasm in adults and is associated with a dismal prognosis. The current standard of care is surgical resection followed by radiation therapy (RT) and concomitant and adjuvant temozolomide (TMZ) chemotherapy [1]. Bevacizumab, an anti-vascular endothelial growth factor (VEGF) agent, has been recently approved for recurrent glioblastoma.

With the standardization of treatment around surgery/RT/TMZ and the current use of bevacizumab, certain patterns that were not previously noticed are beginning to emerge. These changes in magnetic resonance (MR) imaging can



1 **Pseudoprogression**. 59-year-old male, GBM treated with surgery followed by chemotherapy and radiotherapy. Just one month after finishing the treatment the lesion increased in size. The chemotherapy was continued and the lesion decreased in the follow-up exams.

have an impact on individual patient care and on clinical trials of new therapies (alguma referencia).

Pseudoprogression

Pseudoprogression is a subacute treatment-related reaction, usually associated with asymptomatic patients [2]. Shortly after completion of RT, predominantly within the first 3 months, patients with high-grade brain tumors can present with an increase in contrast-enhancing lesion size, mimicking tumor progression, followed by subsequent improvement or stabilization without any further treatment [3, 4].

Pseudoresponse

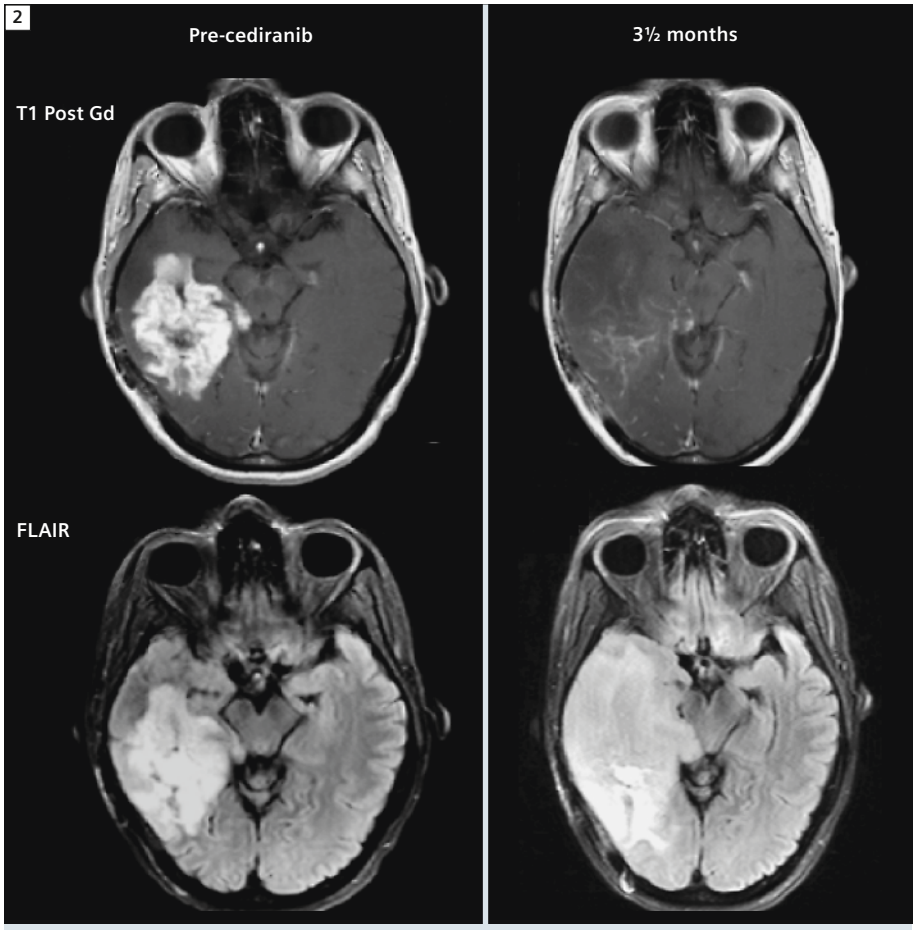
Pseudoresponse is a rapid decrease in contrast enhancement observed in recent high-grade glioma treatment trials after administration of antiangiogenic agents such as bevacizumab and cediranib, a VEGF receptor tyrosine kinase inhibitor [5]. These agents produce a high response rate and 6-month progression-free survival, but with rather modest effects on overall survival.

Mcdonald Criteria

The Macdonald Criteria [6] are currently the most widely used guideline for assessing response to therapy in patients with high-grade gliomas. According to the Macdonald Criteria, tumor progression is considered to have occurred when an increase of 25% in the size of the contrast-enhancing lesion is observed. There are important limitations to these criteria, since they address only the contrast-enhancing component of the tumor, which is nonspecific and may not always be considered a true surrogate of tumor response.

Pathophysiology

Pseudoprogression is found to correspond to gliosis and reactive radiation-induced changes without evidece of viable tumor [6]. It may represent an exaggerated response to effective therapy, involving early changes to the vascular endothelium and the blood-brain barrier (BBB), causing new or increased contrast enhancement on MR imaging examinations. Most importantly, some studies have found an association between the incidence of pseudoprogression and in creased survival; perhaps pseudoprogression represents an active 'inflammatory' response against the tumor [4]. The early decrease in contrast enhancement seen in pseudoresponse suggests a change in vascular permeability, with a 'normalization' of the BBB, rather than a true tumor reduction, as being the underlying cause of the improvement [7]. Normalization of the BBB and subsequent reduction in the vasogenic edema can result in an improvement of symptoms [8, 9].



2 **Pseudoresponse**. An enhancing expansive lesion is demonstrated after treatment failure with concomitant radio and chemotherapy. After initiation of antioangiogenic treatment, a marked decrease in the enhancing portion of the lesion is seen. However, a clear expansion of the lesion can be seen

O6-Methylguanine DNA MGMT promoter

The methylation status of the methyltransferase (MGMT) promoter has been shown to be a potent prognostic factor in patients with GBM; cells that are deficient in MGMT have shown an increased sensitivity to TMZ. Furthermore, MGMT promoter status may predict pseudoprogression in ~90% of patients with methylated glioblastoma [10], due to higher sensitivity to treatment [4] and an approximately 60% probability of early true tumor progression was observed in un- methylated MGMT promoter tumors [11]. Thus, we can speculate that methylated MGMT may be a good indicator of therapeutic response and better prognosis, as an increased overall survival rate has been observed in these patients.

Advanced MR imaging techniques

No single imaging technique has been validated to recognize and adequately establish a diagnosis of pseudoprogression [12] and the diagnosis should depend on follow-up scans until an improved method is established.

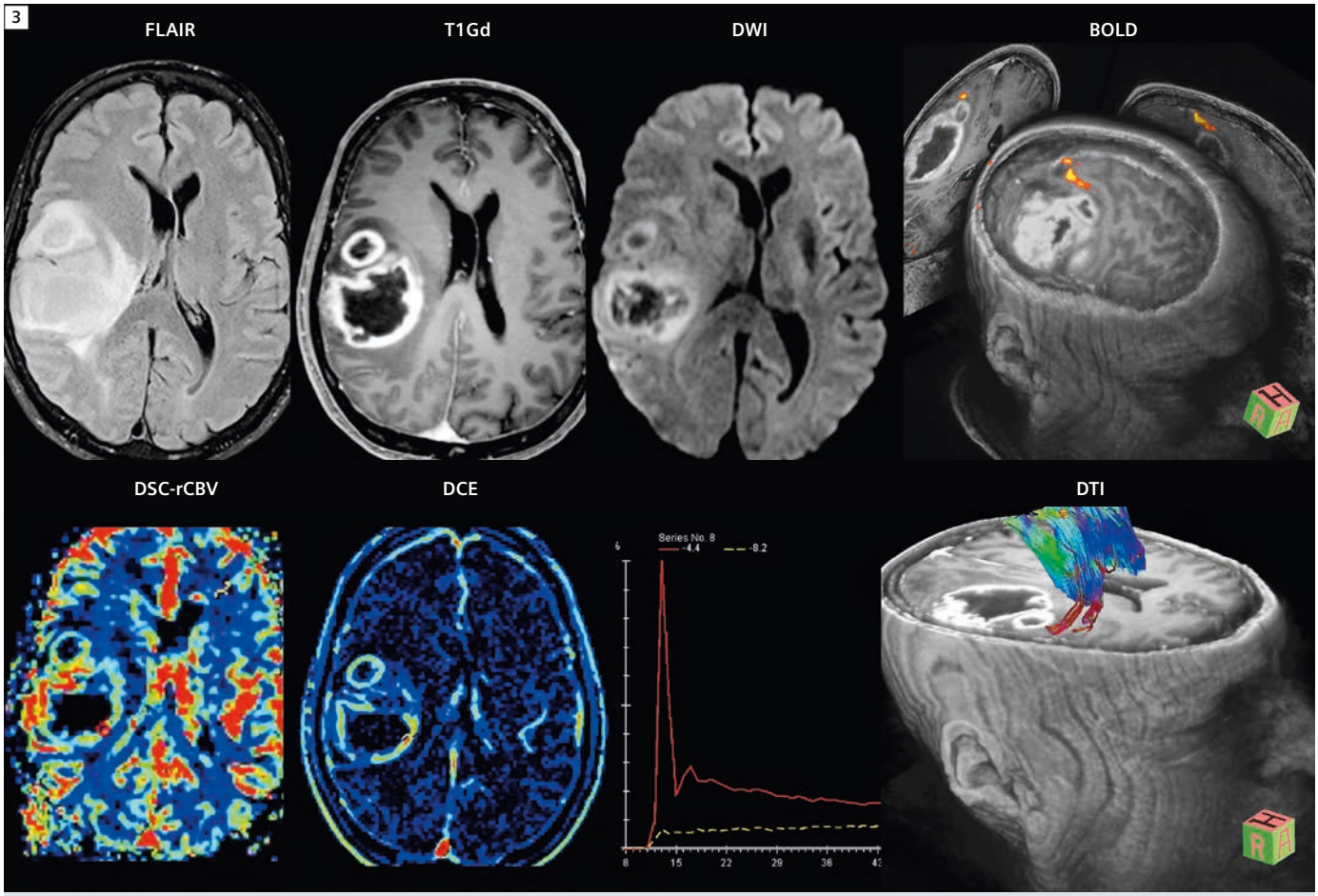
Dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging (DSC) is a surrogate marker for angiogenesis and has been used to assess brain tumor treatment response with high sensitivity for distinguishing residual/recurrent neoplasm from radiation brain injury [13–15].

Permeability DSC is also a potential new tool for differential diagnosis between pseudoprogression and true tumor progression. Although no prospective study has examined this hypothesis, preliminary results with this new technique seem very promising, and a number of clinical trials are underway to better delineate the performance of all of the above techniques.

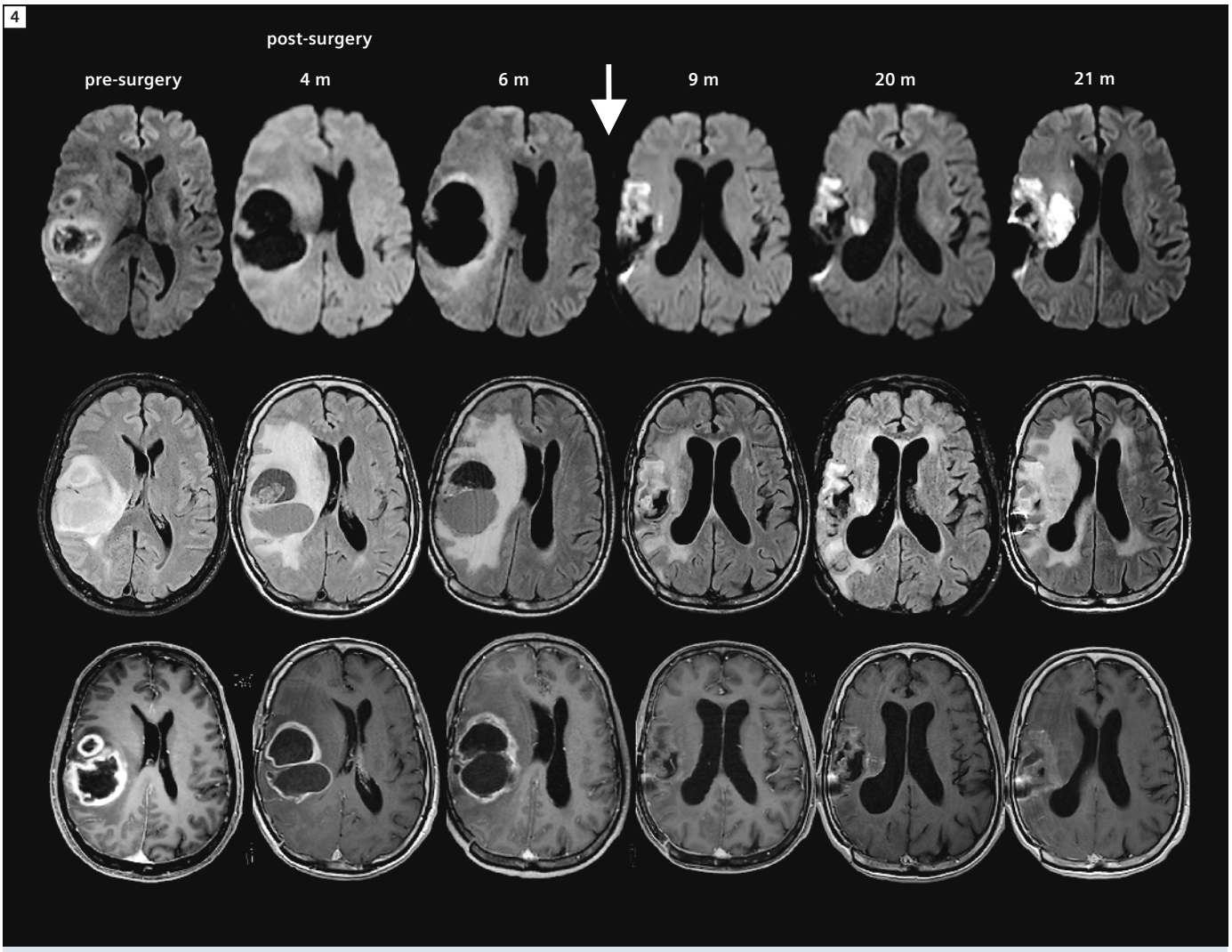
Other techniques, such as MR spectroscopy, diffusion-weighted imaging (DWI) and diffusion tensor imaging (DTI) have been assessed to differentiate tumor progression and/or residual tumor from necrosis [11, 16]. In short, none of them provides sufficient information for differential diagnosis between pseudoprogression and true tumor progression.

Management

Pseudoprogression may influence the clinical recommendation to continue with adjuvant chemotherapy rather than the change to a second-line therapy for recurrence [17]. Currently, the only method of distinguishing pseudoprogression and early progression of disease is to perform follow-up examinations of the patients, since conventional MR imaging is unable to differentiate them and alternative techniques have not yet been validated in prospective trials [4, 11]. Analysis with follow-up conventional MR imaging examinations allows such a distinction because the changes related to pseudoprogression decrease in size. If a post chemoradiotherapy follow-up MR imaging examination demonstrates complete or partial response or stable disease (i.e. smaller or stable tumor enhancement), maintenance of chemotherapy is typically continued. When enlargement occurs, then the treating



3 58-year-old male, GBM. In the first MR exam, an expansive necrotic lesion is demonstrated, with areas of restricted diffusion, hperperfusion and high permeability. Presurgical planning could also be made by using functional MRI analysis using BOLD and tractography sequences to demontrate the relationship with eloquent areas.



4 After failure of the concomitant radio and chemotherapy, second line treatment with antiangiogenic drug was indicated. Just after the initiation of anti-VEGF therapy, a reduction in the contrast enhancing area was seen. Besides a continuing reduction in the enhancing portion of the lesion, an expansion is observed in the FLAIR sequence. However, diffusion images demonstrate an area of restricted diffusion, which may correspond to areas of tumor dissemination, and which may lead to new areas of contrast enhancement.

physician does face a dilemma. If pseudoprogression is suspected, perhaps based on MGMT status and/or very early changes in imaging features in the first months post treatment, ongoing chemotherapy with TMZ might be continued, with close monitoring. In clinically symptomatic patients, more options must be considered, including cessation of therapy, addition of anti-VEGF treatment, or even surgery, since identical symptoms can be observed in patients with true tumor progression and patients with pseudoprogression [8].

Conclusion

Pseudoprogression and pseudoresponse are abnormalities that have been described following high-grade tumor treatment, and remarkably both appear to be associated with future favorable patient outcome. Both phenomena appear to be best diagnosed through follow-up scans because no established method of imaging is yet capable of yielding a definitive diagnosis of true tumor versus enhancement changes due to other reasons. DSC and other methods appear promising but require further testing in the multicenter setting.

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