CASE REPORT

5-aminolevulinic acid guidance during awake craniotomy to maximise extent of safe resection of glioblastoma multiforme

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SUMMARY

Overall survival for patients with glioblastoma multiforme (GBM) has been consistently shown to improve when the surgeon achieves a gross total resection of the tumour. It has also been demonstrated that surgical adjuncts such as 5-aminolevulinic acid (5-ALA) fluorescence—which delineates malignant tumour tissue—normal brain tissue margin seen using violet-blue excitation under an operating microscope—helps achieve this. We describe the case of a patient with recurrent left frontal GBM encroaching on Broca's area (eloquent brain). Gross total resection of the tumour was achieved by combining two techniques, awake resection to prevent damage to eloquent brain and 5-ALA fluorescence guidance to maximise the extent of tumour resection. This technique led to gross total resection of all T1-enhancing tumour with the avoidance of neurological deficit. The authors recommend this technique in patients when awake surgery can be tolerated and gross total resection is the aim of surgery.

BACKGROUND

It is well established that overall survival for patients with glioblastoma multiforme (GBM) is improved when the surgeon achieves gross total resection of the tumour. It has also been shown that surgical adjuncts such as 5-aminolevulinic acid (5-ALA) fluorescence help achieve this. However, there is a concern that this technique may tempt the surgeon into an overly aggressive resection with consequent neurological deficit for the patient. We describe what we believe to be the first case in the literature of combining 5-ALA to maximise the extent of resection of a GBM with awake craniotomy to help minimise the risk of damage to eloquent areas of the brain.

CASE PRESENTATION

A 32-year-old right-handed woman initially underwent debulking of a left frontal GBM in July 2012 and then went on to complete Stupp-protocol chemoradiotherapy. She represented 16 months later with a short history of mild headaches. On review by our speech and language specialist therapist, there were subtle word-finding difficulties in function though not in assessment tasks.

INVESTIGATIONS

MRI of her head demonstrated a recurrence of the tumour in the left frontal lobe encroaching on Broca's area (figure 1A). This proximity of motor

speech areas to the recurrent tumour was confirmed with functional MRI (figure 1B).

TREATMENT

Following neurooncological multidisciplinary team review, the patient was started on dexamethasone, which improved her symptoms.

The patient received 1.5 g of 5-ALA (*Gliolan*, medac GmbH) 6 h prior to the induction of general anaesthesia (GA). She underwent a craniotomy and partial debulking of the lesion while under GA. She was then woken-up and the cortical surface was mapped. It was clear that the fluorescing portion of the tumour was remote from the speech areas. The remaining tumour was debulked while the patient's expressive speech functions were monitored by our speech and language specialist therapist. Carmustine wafers were inserted at the end of the procedure.

OUTCOME AND FOLLOW-UP

The patient suffered no recurrence or exacerbation of her word-finding difficulties; there were no neurological complications. Postoperative MR confirmed a gross total resection of the T1-enhancing tumour (figure 1C). The patient developed a pseudomeningocele that resolved after a short period of lumbar cerebrospinal fluid drainage.

DISCUSSION

To the best of our knowledge, we describe the first use of 5-ALA fluorescence guidance during awake craniotomy. 5-ALA-induced fluorescence is based on the principle that malignant tissue synthesises and accumulates fluorescent porphyrins after administration of 5-ALA, and that this fluorescence can be selectively seen with an operating microscope using violet-blue excitation. It is becoming increasingly used to guide malignant tumour resection.¹ A phase III clinical trial conducted by the European Organisation for Research and Treatment of Cancer (EORTC) has shown that, compared to conventional white-light surgical resection, 5-ALA-induced fluorescence-guided surgery was associated with a higher rate of GTR (65% vs 36%) and progression-free survival at 6 months (41% vs 21%).²

While the EORTC trial showed no additional complications in the 5-ALA group, 5-ALA-guided tumour surgery aimed at gross total resection is more extensive and likely to carry a higher risk of neurological injury. Combining 5-ALA-guided

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Figure 1 (A) Preoperative T1-weighted MRI with contrast. (B) Preoperative T1-weighted (without contrast) functional MRI while testing speech activations. (C) Postoperative T1-weighted MRI with contrast showing complete excision of all enhancing tumour.

surgery with awake craniotomy provides the surgeon with the confidence to maximise the resection while minimising the risk of neurological injury.

For tumours in eloquent areas, it has been shown that awake cortical mapping—the gold standard—can be integrated with intraoperative MRI technology to perform a maximal EOR while avoiding injury to eloquent brain with patients reported to have tolerated the combined procedure well.¹ However, combining an awake craniotomy in an intraoperative MRI suite can be challenging: patient comfort, appropriate sterile draping and redraping and airway access, are some of the problems that prolong surgery and may compromise patient safety. These challenges are avoided with the use of 5-ALA fluorescence guidance and highlight its potential advantages over intraoperative MRI.

Usually, the enhancing lesion of glioblastoma can be identified under white light using an operative microscope. In this regard, the merit of 5-ALA is to detect the tumour cells that have a subtle enhancing effect and that are located in the border zone. The merit of awake craniotomy with cortical and subcortical mapping is to detect a functional area located within or in close proximity to the tumour, especially a non-enhancing tumour, which is difficult to identify under the white light of the operative microscope.

In the present case, the eloquent Broca's area (motor speech function) was located in very close proximity to the subtle and non-enhancing tumour, and surrounding perilesional oedema (figure 1B). Intraoperative 5-ALA fluorescence was able to detect the well-enhancing lesion and the subtle-enhancing border zone. Since functional MRI demonstrated its proximity to Broca's area, and given the aim of extended tumour resection beyond the well and subtle enhancing lesion to include non-enhancing lesion, it was essential that simultaneous cortical mapping was performed in order to guide safe resection and avoid neurological deficit.

It is now well established that 5-ALA staining of glioblastoma tumours appears with peculiar features such as intense fluorescent regions surrounded by pink shaded tissues until reaching the blue normal brain. Complete tumour debulking was achieved by removal of the intensely fluorescing area as well as the subtle fluorescing pink area (figure 2).

The limitation of this technique is the partial resection of the T2-bright signal on fluid attenuation inversion recovery (FLAIR) sequences. It is debated whether this represents further tumour or perilesional oedema. Certainly in this case, not all the T2-bright signal on FLAIR was completely resected.

Figure 2 (A) Intraoperative view of surgical field under white light (dotted line represents resection margin). (B) Intraoperative view of surgical field using 5-aminolevulinic acid fluorescence under violet-blue excitation. The resection margin (dotted line) encompassed the intense fluorescing area as well as the surrounding subtle pink-shaded tissue, but not the blue normal brain.

Patient's perspective

I was excited and nervous about the fact that the surgeons would be using a new technique of dye injection and awake surgery to treat my tumour. During surgery, I concentrated on what the others in the operating room were doing and what they were asking, I remember anxiously waiting for the first task. I felt very little pain during the surgery. I felt very reassured during the operation as the neurosurgeon and operating room staff regularly updated me on exactly which stage of the operation we were at. I was able to speak directly to the neurosurgeon and often received positive feedback from him. I also listened to the staff speaking to each other. This was very reassuring because it helped me remain in control. I was surprised to feel so well after the awake craniotomy—I did not have any typical postsurgery symptoms such as vomiting, nausea, or pain. However, I did feel tired, as though I had done a full day of work. I was relieved to meet my family after the operation and return to some form of normality. I did not feel that my speech was any different after the operation compared to before the operation and that was a relief.

Contributors RC was the primary surgeon and the consultant in charge of the patient's care, and significantly contributed to the writing of the manuscript and critically revised it for intellectual content. SM was significantly involved in performing the literature review, and contributed to analysis and writing of the manuscript, and revised it for intellectual content. AJ is a highly specialist speech and language therapist who provided the preoperative, intraoperative and postoperative speech assessments, and critically revised the manuscript for intellectual content. GS was the second operating surgeon who provided expertise in

Learning points

- ▶ Intraoperative use of 5-aminolevulinic acid fluorescence is important to identify the well-enhancing lesion and its subtle-enhancing border zone. Awake cortical mapping is important to identify functionally eloquent brain in close proximity to the tumour boundary.
- ▶ An approach to high-grade tumour resection incorporating both awake craniotomy and 5-ALA fluorescence guidance can lead to a favourable postoperative outcome in terms of maximising extent of tumour resection without neurological deficit.
- ▶ The authors recommend combining these techniques in patients when awake surgery can be tolerated and gross total resection is the aim of surgery.

performing the awake craniotomy, significantly contributed to the writing of the manuscript, and critically revised it for intellectual content. All authors read and approved the final manuscript.

Competing interests None declared.

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