Heparin-induced tumour bleed

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SUMMARY

Patients with gliomas are at risk for deep vein thrombosis and thromboembolic events, and pharmacological prophylaxis may be indicated. This recommendation needs to be weighed against the risk of spontaneous haemorrhage from certain brain tumours. A patient, who was hemiparetic owing to a high-grade glioma and was started on heparin prophylaxis, developed a tumour bleed. The relevant issues are briefly discussed.

BACKGROUND

Thromboembolic (TE) events secondary to deep venous thrombosis (DVT) are some of the leading causes of death in patients with cancer.¹ Patients with brain tumours are at a high risk of thrombosis and embolism similar to patients with extracranial malignancies; those with high-grade gliomas are at the highest risk.² This risk is significantly increased if the patient has a focal neurological deficit with a paralysed limb(s).³ Primary prevention of TE events with pharmacological agents is therefore recommended in all cancer patients hospitalised for surgical or medical reasons.^{4 5}

Although studies recommend the use of DVT prophylaxis in patients with malignant gliomas, there are other issues to consider. It is a well-known fact that certain brain tumours have a propensity to bleed. Anticoagulation in the early postoperative period in a patient with a partially resected brain tumour may theoretically increase the risk of haemorrhage from residual tumour, although this risk would probably be outweighed by the benefits of anticoagulation. However, the risk of heparin-induced haemorrhage from an unresected tumour is not known and has not been reported. A patient who developed a large heparin-induced bleed from an unresected tumour is reported here.

CASE PRESENTATION

A 45-year-old lady presented with a history of progressively worsening headache and weakness of the left upper and lower limbs for 3 months. On examination, she was conscious, alert and oriented. Fundus examination revealed bilateral papilloedema. She had left hemiparesis with power grade 2/5 in the upper and lower limbs. MRI of the brain revealed a right medial frontal cingulate lesion with solid and cystic components. The solid component was isointense on T1-weighted images (WI), iso to hyperintense on T2 and FLAIR (fluid attenuated inversion recovery) WI and enhanced on gadolinium contrast sequences (figure 1). There were foci of low signal susceptibility on gradient echo images, suggesting areas of bleed (or calcification). Surrounding this solid area was a cyst whose contents were T1 hypointense, T2

hyperintense and did not invert with cerebrospinal fluid on FLAIR images (figure 1C). Free diffusion was seen in this cystic area. The wall of the cyst faintly enhanced on contrast administration. Significant peritumoural oedema extending into the centrum semiovale was seen (figure 1D).

Right frontal parasagittal craniotomy followed by an interhemispheric approach and excision of the lesion was planned. After induction of general anaesthesia, internal jugular and radial arterial lines were secured. The patient was positioned supine with the head elevated and flexed, and rigidly fixed in a three-pin fixation system. The craniotomy flap was raised and the dura was opened based on the superior sagittal sinus. At this point, brain bulge developed and, despite aggressive attempts by the anaesthesia team which included the administration of mannitol, steroids and hyperventilation, the brain bulge continued to worsen. This made it impossible to dissect the parasagittal draining veins and enter the interhemispheric fissure. The procedure was abandoned and the incision closed in layers. The dura was not closed and the bone flap was not replaced. An immediate CT scan was performed to rule out any pin-site extradural haematoma (EDH). However, this was not seen and CT revealed persistent hemispheric oedema and no fresh haematoma (figure 2A,B).

The patient was fully conscious and could be extubated on postoperative day 1. Power in the left upper and lower limbs had worsened to grade 1/5. Active limb physiotherapy was instituted. On postoperative day 3 (more than 72 h after the surgery), she was started on 0.2 ml subcutaneous injection, twice a day, of low molecular-weight heparin. She continued to remain neurologically stable, was fully conscious and alert. On postoperative day 7 (5 days into heparin therapy), she became drowsy and gradually lapsed into altered sensorium (GCS E1 M4 Vt). Examination revealed anisocoria with the right pupil being dilated and non-reactive.

INVESTIGATIONS

Repeat CT at this time showed a large intracerebral haematoma dissecting superolaterally from the tumour. There was significant mass effect and midline shift due to the haematoma (figure 2C). Platelet count, prothrombin time with international normalised ratio (PT INR) and haemogram were normal at this time.

TREATMENT

Emergency re-exploration was performed. The haematoma had surfaced over the superior frontal gyrus and was evacuated. At the inferomedial limit of the haematoma, a greyish, soft and vascular lesion was encountered and this was decompressed.

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Figure 1 Preoperative MRI. (A) T2-weighted image, coronal view showing a lesion with heterogeneous solid and peripheral T2 hyperintense components with extensive perilesional oedema. (B) T1 postcontrast image, sagittal view showing enhancement of the solid component. (C) Fluid attenuated inversion recovery axial image demonstrating that the T2 hyperintense cyst does not invert. (D) Demonstrates the difference in diffusion parameters between the solid and cystic components.

She recovered gradually from surgery and by postoperative day 3, she was weaned off ventilator and extubated; left-sided hemiplegia persists.

Histopathological examination of the resected lesion revealed a cellular tumour composed of neoplastic glial cells with vesicular monomorphic nuclei and clear cytoplasm capping the cortex.

Immunohistochemistry revealed glial fibrillar acidic protein positivity highlighting the pericellular stroma and a high MIB-1 labelling index (10–12%) (figure 3). These features were diagnostic of anaplastic oligodendroglioma, WHO grade III. Postoperative CT revealed near total excision of the lesion and haematoma (figure 2D).

OUTCOME AND FOLLOW-UP

Adjuvant therapy was planned but refused by the family and patient. Six months postsurgery, she remains conscious and alert, right-side power has improved to grade 4/5.

DISCUSSION

This patient presented with headache and hemiparesis owing to a right medial frontal lesion. MRI revealed an enhancing tumour with solid and cystic components with small areas of haemorrhage within the tumour. At the first surgery, the lesion

could not be accessed or decompressed owing to the development of severe brain bulge soon after craniotomy. The causes responsible for the severe and acute brain bulge are thought to be a possible exaggeration of pre-existing tumour-related oedema and possibly, catheterisation of the ipsilateral internal jugular vein. The CT did not reveal any fresh haematoma related to the tumour or sites of pin fixation.

Since the patient had significant weakness of her left upper and lower limbs, it was decided to institute heparin therapy for DVT prophylaxis more than 72 h postoperatively. The patient remained stable for 5 days after the institution of heparin therapy and then developed a massive tumour bleed, with no other immediate precipitating factor.

Patients undergoing surgery for brain tumours have a high risk of DVT and pulmonary TE.¹ Many factors may be responsible for this, including postoperative immobilisation, paresis of limbs leading to impaired or sluggish venous outflow, steroid medications that are almost universally employed in such patients and the release of tissue factor and other procoagulants by the tumour itself.² A large retrospective population-based study found that among 9489 cases of malignant glioma, the incidence of venous TE was 16.1 events/100 person-years during the first 6 months, with 55% of the cases diagnosed within 61 days after a craniotomy.³ This risk is increased in patients with

Figure 2 (A and B) Immediate postoperative CT image showing peritumoural oedema. (C) Large haematoma that developed on postoperative day 7 (day 5 of low-molecular-weight heparin therapy). (D) CT showing near total evacuation of the haematoma and decompression of the lesion.

limb weakness leading to immobility of one or more limbs. Thus, primary prevention with pharmacological agents is recommended in all patients with gliomas who have limb weakness. The increased risk of TE exists not only in the perioperative period but extends to the period during which adjuvant therapy (especially radiotherapy) is administered and well beyond.⁴ It has also been shown that patients who undergo biopsy or subtotal resection of gliomas are at a higher risk for TE than those who undergo gross total resection.⁵ Some trials assessing anticoagulant prophylaxis in neurosurgical patients have shown no significant increase in bleeding.⁶ A meta-analysis of low-molecular-weight heparin for DVT and TE prophylaxis in neurosurgery found that the number needed to treat (prevent an episode of TE) was 7.7 for thromboembolism and 16 for proximal deep venous thrombosis. The number needed to harm (ie, to produce a major bleed secondary to heparin) was 115. This analysis demonstrated the relative safety of administering low-molecular-weight heparin in selected high-risk patients.⁷

In a postoperative setting, the causes of tumour-related bleed would include a deranged coagulation system and residual tumour that would have a propensity to bleed. Heparin itself is known to cause thrombocytopenia in an idiosyncratic manner, and this could precipitate a tumour bleed.⁸ In the current

instance, all haematological parameters were within normal limits at the time of the bleed. Besides, the tumour itself had not been accessed at the time of surgery. This leads to the conclusion that this is an instance of a spontaneous tumour bleed induced by heparin.

We believe that the cause of tumour bleed has more to do with the tumour pathology. Most reported instances of heparin-related tumour bleeds are in patients who have undergone either biopsy or partial resection of tumours or in those who are undergoing adjuvant therapy. Reports of haemorrhage from an unresected tumour precipitated by heparin administration are very uncommon.

Certain brain tumours have a propensity to bleed.^{9–10} A large study of 7373 intracranial tumours and 110 tumour bleeds found the following pathological distribution of bleeds—36 (33%) glioblastomas, 23 (21%) metastases, 14 (13%) anaplastic gliomas, 13 (12%) low-grade gliomas, 13 (12%) meningiomas, 5 (5%) adenomas, 2 (2%) haemangioblastomas, 2 (2%) melanomas, 1 (1%) neuroblastoma and 1 (1%) pinealoblastoma. Grade 1 tumours like pilocytic astrocytoma have been reported to bleed as well.¹¹ Kondziolka *et al*¹² found that the highest haemorrhage rate for primary brain tumours was 29.2% for mixed

Figure 3 (A and B) Photomicrograph reveals an angioma-like zone with conglomerates of large and small ectatic thin-walled veins enclosed in a fibrotic collagenised stroma (A) highlighted by Masson trichrome stain (MAT, B). (C–E) Along the wall of the vasoformative lesion (C, v) a thin strip of neoplastic glial cells are seen with an oligodendroglial morphology (asterix), that are labelled with glial fibrillar acidic protein (GFAP) (D) and show high MIB-1 labelling index (E) confirming the neoplastic nature of the glial cells. Stains: (A) H&E, (B) Masson trichrome, (C) H&E, (D) GFAP immunoperoxidase, (E) MIB-1 immunoperoxidase (magnification, scale bar).

oligodendroglioma/astrocytoma, whereas the highest haemorrhage rate for any tumour type was 50% for metastatic melanoma.

The histopathology of the tumour in the present instance revealed it to be an anaplastic oligodendroglioma. This tumour was of high grade and of oligodendroglial lineage. Preoperative MRI showed small foci of previous haemorrhage within the tumour. This was confirmed at histopathological examination where ectatic vessels and old microbleeds with haemosiderin deposits were seen. These factors probably made it a high-risk lesion for haemorrhage.

There is a definite role for the administration of low molecular-weight heparin in patients who are at high risk for DVT and TE. The high-risk factors for DVT and TE events include a high-grade pathology, patients who have undergone biopsy or subtotal resection, those who have a paralysed limb and/or a poor Karnofsky performance score. However, if the MRI demonstrates areas of previous haemorrhage and the tumour is of oligodendroglial lineage, the use of heparin should probably be avoided.

Competing interests None.

Patient consent Obtained.

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Learning points

- ▶ Patients with high-grade brain tumours are at high risk for deep vein thrombosis and thromboembolic events.
- ▶ This risk is increased in those with limb weakness, partially resected tumours and during the time of administering adjuvant therapy.
- ▶ Pharmacological prophylaxis may be indicated in these patients.
- ▶ In those patients whose MRI raise the suspicion of intralesional haemorrhage or in those where the perilesional oedema is disproportionate to the size of the lesion, anticoagulation should be avoided lest it precipitate a tumour bleed.

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