Reminder of important clinical lesson

Atrial flutter in a patient with glioblastoma multiforme: problems in treating thromboembolic complications

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A 55-year-old gentleman with a left-sided glioblastoma multiforme (GBM) presented with palpitations which were shown to be atrial flutter (AFL) on ECG. Approximately 6 h later, he developed ataxia and expressive dysphasia. A brain CT scan showed no acute haemorrhage and no progression of the brain tumour. Ischaemic stroke was the top differential diagnosis. However, the authors could not perform thrombolysis due to the risk of intratumour haemorrhage. The AFL reverted to sinus rhythm with metoprolol and digoxin after 3 days. His neurological signs resolved within 24 h, and a diagnosis of transient ischaemic attack secondary to AFL was made. This case highlights the challenge of managing thrombo-embolic complications of arrhythmias in cancer patients.

BACKGROUND**Glioblastoma multiforme**

Glioblastoma multiforme (GBM) is a primary brain tumour originating from astrocytes.¹ It is classified as grade IV under the WHO classifications, making it one of the most aggressive primary tumours of the brain.² GBM can manifest itself in a variety of ways, including headaches, focal neurological signs as well as seizures. The mainstay of treatment includes surgery with radiotherapy and chemotherapy.³ Despite treatment, GBM carries a poor prognosis with 5-year survival reported to be less than 5% in some studies.²

Atrial flutter

Atrial flutter (AFL) is a macroreentrant atrial tachycardia. It is the commonest atrial tachycardia, second only to

atrial fibrillation (AF).⁴ AFL is characterised by a rate of ≥ 240 beats/min in the absence of an isoelectric baseline between deflections.⁵ AFL is usually not life threatening but can be associated with impaired myocardial perfusion, hypotensive episodes and cardiomyopathy.⁶ The management of AFL is similar to that of AF and has four areas of consideration: reversion to normal sinus rhythm (NSR), maintenance of NSR, ventricular rate control and thromboembolic prophylaxis. The 2006 American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) guidelines recommend the use of oral β -blockers, digoxin or amiodarone for ventricular rate control in AFL.⁷ Methods available for reversion to NSR include both electrical and pharmacological cardioversion.⁷

Figure 1 ECG performed on admission shows atrial flutter (AFL) at a rate of 158 beats per minute.

Figure 2 Chest x-ray on admission. The postero-anterior radiograph is unremarkable. There are no signs of intrathoracic mass lesions which could cause compression of the atria.

Thrombo-embolic complications of AF

Much like AF, AFL causes stasis of blood in the atria, leading to thrombi formation and subsequent downstream embolic strokes. Such strokes can be managed with thrombolysis in the acute setting and need appropriate thromboprophylaxis in the long term.⁷ Thrombolysis with alteplase, a recombinant tissue-plasminogen-activator, is known to improve the outcomes and prognosis of ischaemic strokes if given within 3 h after onset of symptoms.⁸ The major risk of thrombolysis is intracerebral haemorrhage,⁸ which is complicated with the added risk of intratumour haemorrhage if a brain tumour is present.⁹ Furthermore, ACC/AHA/ESC recommends anticoagulation prophylaxis in AFL patients with thrombo-embolic complications.

CASE PRESENTATION

A 55-year-old white man diagnosed with an aggressive left-sided GBM 1 year previously presented with a 2-h history of palpitations. His GBM was treated with radiotherapy 6 months ago, and at the time of presentation he had completed his second 3-monthly surveillance MRI scan, which showed stable disease. Nevertheless, he was managed palliatively given the aggressive natural of his GBM. He was otherwise well with no history of cardiovascular disease. He had an unremarkable family history and is a non-smoker and non-alcohol drinker. He takes lansoprazole for mild heartburns. Observational findings are as follows: pulse fluctuating between 150 and 160 and irregular, blood pressure 177/98, oxygen saturation 96% on room air and auricular temperature was 36.5°C. Examination was otherwise unremarkable.

An initial ECG showed AFL at 158 per minute (figure 1) and 5 mg of metoprolol was given intravenously

immediately, followed by a loading dose of oral digoxin 500 µg. A repeat ECG in 15 min still showed AFL at 150 per minute, and he was given regular metoprolol and digoxin. Around 6 h later, he developed sudden onset unsteadiness while standing and was transferred to the high-dependency unit (HDU). On examination, he had new onset expressive dysphasia and bilateral up-going plantars. Neurological examination was otherwise unremarkable with normal tone, power, reflexes and sensation bilaterally. Chest was clear, heart sounds were normal, and his abdomen was soft and non-tender. There were no major changes in his observations, and he was still in AFL.

INVESTIGATIONS

Initial blood tests were as follows: haemoglobin 13.4 g/dl, white cell count $5.4 \times 10^9/l$, platelets $211 \times 10^9/l$, sodium 135 mmol/l, potassium 4.3 mmol/l, urea 6.8 mmol/l, creatinine 117 µmol/l, Glucose 6 mmol/l and C reactive protein was 23 mg/l. Urine dipstick was clear. ECG showed AFL as mentioned before, and chest x-ray was unremarkable (figure 2). An urgent CT head was performed which showed no acute intracranial haemorrhage and no progression of the GBM tumour (figure 3). A trans-thoracic echocardiogram (TTE) performed failed to demonstrate any underlying cardiomyopathy, vascular disease or obvious large atrial thrombi. However, the left atrial appendage (LAA), where the majority of intra-atrial thrombi originate from, cannot be assessed with TTE. It can only be visualised with a trans-oesophageal echocardiogram (TOE) or an intracardiac echocardiogram (ICE). Due to facility constraints, neither TOE nor ICE was performed. CHADS2 (congestive heart failure, hypertension, age, diabetes mellitus, stroke) score¹⁰ was zero.

Figure 3 Comparison of a CT brain on admission with an MRI brain 3 months earlier. (A) The MRI scan was taken 3 months before admission. It shows left-sided mass with surrounding oedema and slight midline shift to the right. There is compression of the ventricles on the left. Despite these abnormalities, the patient did not display neurological signs on admission. (B) The CT scan with contrast was done after the onset of neurological signs. It showed no progression of GBM, furthermore, there were no visible haemorrhages.

DIFFERENTIAL DIAGNOSIS

Stroke/transient ischaemic attack (TIA) secondary to AFL was our top differential diagnosis. This was supported firstly by a sudden onset of new neurological symptoms on a background of AFL. Second, we could not rule out the presence of a LAA thrombus. Last, there was no evidence of intracranial haemorrhage or GBM disease progression on the CT scan to account for these neurological signs.

TREATMENT

Management of this patient presented us with a major dilemma. Owing to the increased risk of intracranial haemorrhage and an additional risk of intratumour haemorrhage, we did not perform thrombolysis for the suspect stroke/TIA. He was monitored on a cardiac monitor in our HDU. His AFL was managed with regular intravenous metoprolol and digoxin. We commenced twice daily oral dexamethasone 8 mg as part of his GBM management. He was otherwise treated conservatively.

We referred for a neurologist review, which concurred with our diagnosis of stroke/TIA. Disease progression was unlikely to cause a sudden onset of neurological symptoms. We were recommended to adopt a conservative approach to management with poststroke rehabilitation. We were advised against thrombolysis due to risks of intracerebral and intratumour haemorrhage.

A neurosurgical opinion was sought from our tertiary referral centre. We were advised that the patient was unsuitable for intracranial surgical intervention given the diffuse nature of GBM and his palliative status. Furthermore, he was considered to have a high mortality risk for bore-hole procedures, should haematomas result from thrombolysis or anticoagulation.

OUTCOME AND FOLLOW-UP

Our patient remained in HDU for 3 days. His neurological signs resolved completely around 18 h after onset, and his AFL reverted to sinus rhythm on day 3. A diagnosis of TIA secondary to AFL was made, and he was discharged home with outpatient cardiology follow-up.

DISCUSSION

This was an interesting case for three reasons. First, it demonstrated an unusual and unexpected presentation of AFL in a patient with GBM. Second, it demonstrated the principle that, when presented with new onset neurology in GBM patients, it is important to distinguish between stroke and tumour progression. Last, it highlights the difficulty in managing arrhythmia related thrombo-embolic events in patients with brain tumours.

Atrial flutter and GBM

Brain tumours have very rarely been associated with arrhythmias. Mathew *et al* reported a case of AF in a patient with frontal meningioma in 1970.¹¹ More recently, bradycardia has been reported in a patient with temporal lobe tumour.¹² Interestingly, both cases were associated with epileptic seizures, which were not present in our patient. There are no previous reports of AFL or AF in association with GBM.

AFL occurs secondary to atrial dilatation.⁶ Our patient did not have the 'common' risk factors, such as cardiovascular diseases, hyperthyroidism or respiratory diseases such as pneumonia or pulmonary emboli.⁶ So an association with GBM cannot be ruled out. The question is "How can a brain tumour affect the heart?" The mechanism is unclear, but one theory involves compression of the heart by intrathoracic metastases, leading to arrhythmias. Indeed, AF is known to be induced by external pressure from intrathoracic tumours or masses,^{13–15} and GBM has been shown to metastasise to the thoracic regions such as lymph nodes,¹⁶ lungs^{17 18} and pleura.^{17 18} So on face value, extracranial GBM metastases to the thorax causing arrhythmias is feasible. However, intrathoracic compression of the heart has not been reported to induce AFL and indeed atrial dilatation rather than compression is the chief mechanism in AFL pathogenesis. Furthermore, the actual likelihood of GBM metastasising outside the brain is very low.^{16–18} In hindsight, a thoracic CT looking for metastases at the time of presentation would have been helpful. Overall, the link between AFL and GBM is feasible, although it is more likely purely coincidental.

AFL and the left atrial appendage

AFL is known to cause embolic strokes and TIA. The LAA is the major source of primary thrombi, contributing up to 90% in some studies.^{19–21} TTE cannot visualise the LAA, which is only possible with TOE or, less commonly, ICE. TOE is therefore considered the gold standard imaging tool for this purpose.²² Unfortunately, we were only able to perform a TTE for our patient due to facility restraints, and, although it was normal, we could not rule out a LAA thrombus.

Vascular events versus cancer progression

In the presence of GBM and indeed any intracranial malignancy, it is vital to distinguish between vascular events and disease progression, since one can masquerade as the other.^{23–25} Both haemorrhagic and ischaemic strokes have been reported to present similarly to brain tumours. In this case, it is a good practice to perform a brain CT and compare the disease load with previous imaging.

Thrombolysis and brain tumours

The major learning point to appreciate from this case is the dilemma of treating ischaemic stroke/TIA in the presence of an underlying intracranial malignancy, which is prone to bleeding.^{25–26} This issue was highlighted by a case report in 2007 from Grimm *et al.*⁹ They performed thrombolysis on a patient with new onset stroke which resulted in intratumour haemorrhage of a previously undetected GBM.⁹ In a literature search by Han *et al* in 2006, the estimated risk of thrombolysis-induced haemorrhage in patients with intracranial tumours was 3%.²⁷ However, the authors compared this 3% risk to the mortality risk of untreated unstable pulmonary emboli, which was estimated to be between 25% and 50%. In this case, the authors believed thrombolysis was favourable and stressed the importance of case specific considerations.²⁷ For our patient, we decided against thrombolysis as we felt that the possibility of a catastrophic intratumour bleed outweighed the potential benefits of thrombolysis.

Fortunately, our patient's neurological symptoms resolved and his AFL terminated. Had his arrhythmia persisted, it would bring further management problems regarding stroke prevention with anticoagulation, re-igniting another clot-versus-bleed dilemma.

Learning points

- ▶ GBM is an aggressive type of brain tumour with a poor prognosis.
- ▶ Atrial arrhythmia may occur in patients with brain tumour and cause strokes/TIA.
- ▶ It is important to distinguish between a vascular cause and disease progression whenever a patient with brain tumour presents with new onset neurological signs.
- ▶ Management of strokes/TIA is challenging in patients with brain tumour and need to be considered on a case-by-case basis.

Competing interests None.

Patient consent Obtained.

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