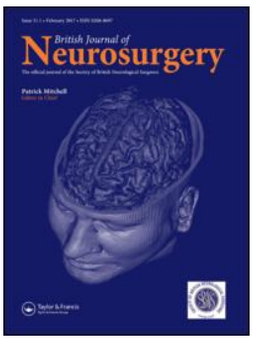

British Journal of Neurosurgery

ISSN: 0268-8697 (Print) 1360-046X (Online) Journal homepage: http://www.tandfonline.com/loi/ibjn20

Glioblastoma multiforme metastatic to lung in the absence of intracranial recurrence: case report

Ashwin Kumaria, Alice Teale, Girish V. Kulkarni, Harshal A. Ingale, Donald C. Macarthur & Iain J.A. Robertson

To cite this article: Ashwin Kumaria, Alice Teale, Girish V. Kulkarni, Harshal A. Ingale, Donald C. Macarthur & Iain J.A. Robertson (2018): Glioblastoma multiforme metastatic to lung in the absence of intracranial recurrence: case report, British Journal of Neurosurgery, DOI: 10.1080/02688697.2018.1529296

To link to this article: https://doi.org/10.1080/02688697.2018.1529296

Published online: 19 Nov 2018.

BRITISH JOURNAL OF NEUROSURGERY
https://doi.org/10.1080/02688697.2018.1529296

Taylor & Francis
Taylor & Francis Group

REPORT

Glioblastoma multiforme metastatic to lung in the absence of intracranial recurrence: case report

Ashwin Kumaria, Alice Teale, Girish V. Kulkarni, Harshal A. Ingale, Donald C. Macarthur and Iain J.A. Robertson

Department of Neurosurgery, Queen's Medical Centre, Nottingham, UK

ABSTRACT

We present the case of a 65 year old gentleman who underwent craniotomy and debulking of a left temporal glioblastoma multiforme (GBM). Post-operatively he received chemotherapy and radiotherapy with good response demonstrated on interval MRI scans. At 17 months post-diagnosis and in the absence of clinical or radiological recurrence, he presented with respiratory distress. He was found to have an exudative right-sided pleural effusion, nodular pleural thickening, a hilar mass and associated lymphadenopathy. Percutaneous pleural biopsy revealed metastatic GBM. Systemic GBM metastasis despite good response to oncological treatments and in the absence of intracranial recurrence is exceedingly rare. We review the literature concerning extra-neuraxial GBM metastasis and speculate why this phenomenon is extremely rare.

ARTICLE HISTORY
Received 3 June 2018
Revised 10 September 2018
Accepted 24 September 2018

KEYWORDS
Glioblastoma metastasis; Extracranial glioblastoma; Glioblastoma multiforme; Brain tumours

Case

A 65 year old gentleman presented with a three week history of progressive headache, dizziness, confusion, poor memory and behavioural changes. On initial presentation he had confusion, receptive and expressive dysphasia, but no other deficits. He had a history of hypertension, hypercholestrolaemia and ischaemic heart disease (previous myocardial infarction and coronary stenting).

MRI brain revealed a solitary large ($45 \times 54 \times 64$ mm) intrinsic cystic/necrotic left temporal lobe tumour with a hypervascular anterior nodule consistent with high grade glioma (Figure 1). There was associated significant vasogenic oedema and, of note, the tumour was seen to blend with the surface of the temporal horn of the lateral ventricle. CT scan of the body did not reveal any abnormality.

He underwent craniotomy and debulking of the tumour with post-operative MRI scans confirming satisfactory debulking of the tumour. Histological analysis revealed an astroglial tumour with high mitotic activity, necrosis and vascular proliferation and a diagnosis of GBM was made. Genotyping revealed that the tumour was IDH-1(Isocitrate Dehydrogenase-1) wild type. He received the Stupp protocol[1] wit good response demonstrated on interval MRI scans and no neurological deterioration.

At 17 months following initial diagnosis he presented with acute shortness of breath. He was found to have a right sided pleural effusion (Figure 2). A chest drain was inserted and analysis of pleural fluid confirmed it was a transudate although no abnormal cells were found. CT of the body revealed pleural based nodular deposits, hilar lymphadenopathy and a mass at the right hilum encasing the right pulmonary artery (Figure 2).

Percutaneous pleural biopsy was carried out. Histological analysis revealed astroglial cells expressing glial fibrillary acidic protein (GFAP). A diagnosis of GBM metastatic to the right lung was confirmed. He died due to respiratory failure shortly thereafter, before palliative oncological treatments could be instituted.

Discussion

Extra-neuraxial spread of GBM is extremely rare. Fewer than 140 such reports exist in the medical literature and include cases of lung, liver, bone, lymph node, spleen, cardiac, orbit, meningeal and surgical seeding/operative flap metastases.[2] Lung metastases were found in around one third of cases, making it the commonest site of metastasis, despite fewer than 45 reported cases.[2] It is possible that less ubiquity and inferior sensitivity of diagnostic imaging in the past may have led to fewer diagnoses and underreporting of this phenomenon. However, virtually all of the reported cases of GBM metastases were in the context of advanced stages of intracranial GBM.[2] We present the rare case of a patient whose intracranial GBM was well controlled following surgery and oncological treatments, but developed lung metastases as a result of which he died.

Owing to the rarity of this condition, it is unclear if overall survival in GBM is decreased in the context of extra-neuraxial GBM metastasis. Available demographic information including age of diagnosis and a male predilection appear to be similar to GBM in general.[2] However, these data are subject to problems with collation of retrospective series including recall bias.

Why is extra-neuraxial GBM spread rare? Firstly, one may argue that the poor prognosis that GBM carries would imply that patients die as a result of GBM before the tumour has an opportunity to metastasise. As above, most cases of extra-neuraxial GBM spread was in the context of end-stage neuraxial GBM. Notwithstanding, an attractive theory suggested that this may be due to the lack of a cerebral lymphatic system.[3,4] However, a cerebral glial lymphatic ("glymphatic") system has recently been described[5] which may challenge this theory. Nonetheless, the suggested glymphatic system is not directly comparable to systemic

CONTACT Ashwin Kumaria Ashwin.Kumaria@doctors.org.uk Department of Neurosurgery, Queen's Medical Centre, Nottingham, NG7 2UH, UK

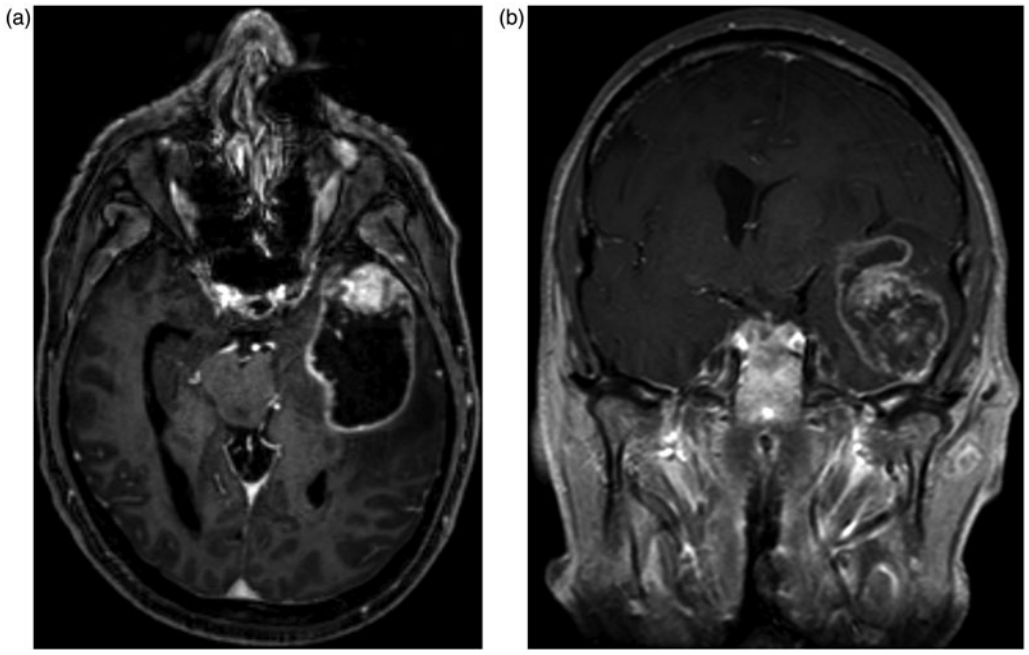

Figure 1. Large intrinsic cystic/necrotic left temporal lobe tumour with a hypervascular anterior nodule. (a) Axial MRI with contrast; (b) Coronal MRI with contrast.

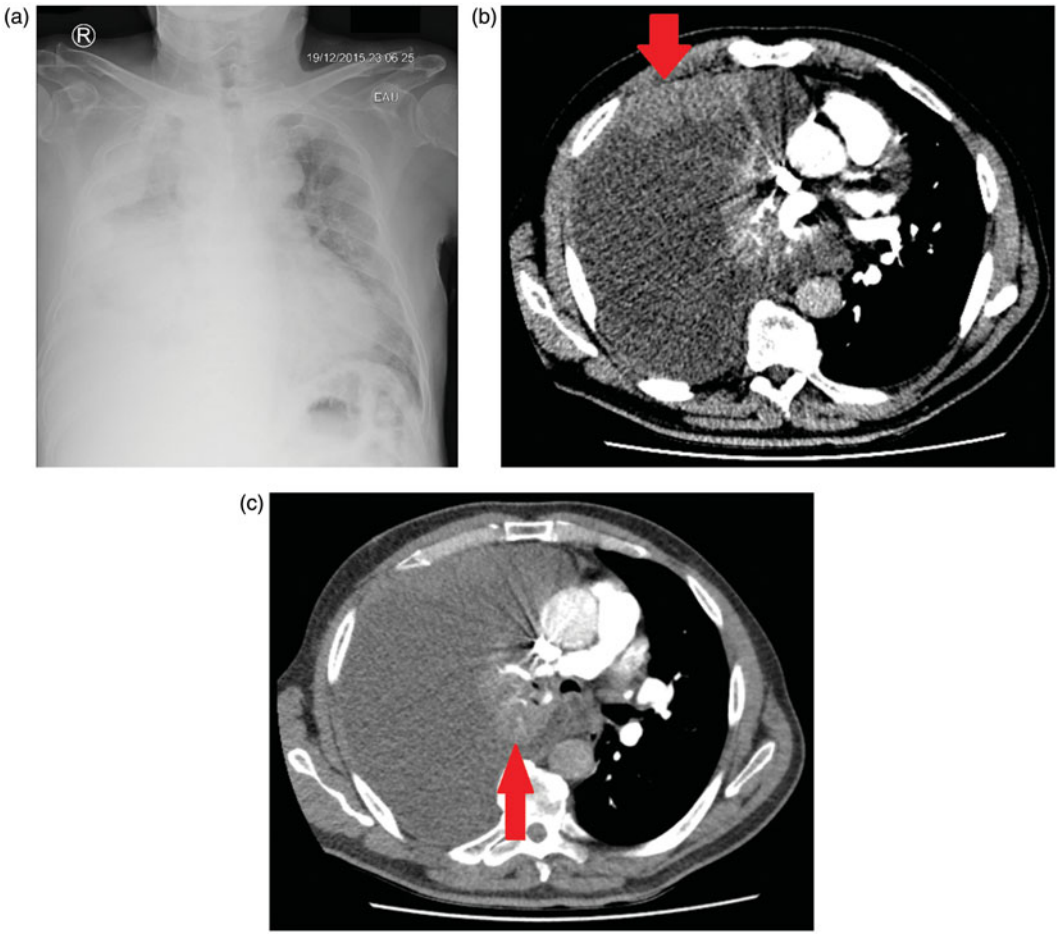

Figure 2. Pleural effusion associated with hilar mass and pleural metastasis. (a) Chest radiograph showing large right sided pleural effusion; (b) CT chest with contrast showing pleural metastasis (arrow); (c) CT chest showing right hilar mass (arrow).

lymphatics for a number of structural and functional reasons[6] and more remains to be learned about the role of glymphatics and GBM.

A haematogenous route for extra-neuraxial spread is another possibility. In our patient, the tumour was in a region with extensive venous drainage including the middle cerebral veins, sphenoparietal sinus and cavernous sinus. Traditionally, haematogenous spread of GBM was considered unusual as intracerebral veins are thin walled and would probably collapse from compression prior to tumour invasion.[2] Similarly, transneural spread of GBM metastases along cranial and peripheral nerves is also reported,[2,4] although this route may not apply to our case.

Dissemination of GBM cells via CSF is a possibility and metastasis associated with CSF shunts has been reported. Indeed, on pre-operative imaging the tumour was seen to blend with the surface of the temporal horn of the lateral ventricle. On the other hand, if spread through CSF pathways was commonplace then one would expect distant GBM spread to non-contiguous structures within the neuraxis, for example from supratentorial to infratentorial structures to be common, but these too are rare.[7] Distant neuraxial spread remains but an exceptional phenomenon.

In other words, GBM has a low tendency for distant spread both within and without the neuraxis. To apply the prevailing self-seeding model of metastasis here,[8,9] tumorigenic cancer stem cells – which possess the ability to generate all cell types in a particular cancer – may be implicated.[10] In the context of GBM, cancer stem cells have been elusive and remain to be conclusively characterised.[11] Ultimately, a better understanding of brain tumour stem cell biology may shed further light. Conversely, perhaps brain tumour stem cells' reduced propensity for distant spread may help us understand better GBM biology in the future.

Furthermore, distant GBM spread probably has a genetic propensity, as has been demonstrated in other cancers.[12] At present there are no known genes that may play a role in GBM metastasis although certain genes which have a role in prognostication (e.g. IDH-1/IDH-2) may be implicated. Our patient was IDH-1 wild type and this is the first description of extra-neuraxial GBM metastasis with genotyping information. Further studies in this area are indicated and DNA methylation-based diagnostic studies may provide useful information.[13]

Conclusion

We present the rare case of GBM metastatic to lung. The patient died as a result of respiratory failure secondary to pleuropulmonary metastatic disease despite good response of the temporal tumour to oncological treatments in the absence of clinical or radiological recurrence. Previously reported GBM metastases have been in the context of advanced primary GBM.

This case adds to the small body of literature surrounding GBM metastasis. We speculate on reasons why this phenomenon is rare including the role of glymphatic, haematogenous and CSF-borne GBM spread models as applied to this case.

Why distant GBM spread is rare may, in the fullness of time, improve our understanding of GBM in general. Metastases require seeding of a tumorigenic stem cell which is as yet partially understood in the case of brain tumours. Further research into GBM biology and genetics will ultimately test the above hypotheses.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

1. Stupp R, Mason WP, van den Bent MJ, *et al.* Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005;352:987–96.
2. Piccirilli M, Brunetto GM, Rocchi G, Giangaspero F, Salvati M. Extra central nervous system metastases from cerebral glioblastoma multiforme in elderly patients. Clinico-pathological remarks on our series of seven cases and critical review of the literature. *Tumori* 2008;94:40–51.
3. Terheggen HG, Müller W. Extracerebrospinal metastases in glioblastoma. Case report and review of the literature. *Eur J Pediatr* 1977;124:155–64.
4. Utsuki S, Tanaka S, Oka H, Iwamoto K, Sagiuchi T, Fujii K. Glioblastoma multiforme metastasis to the axis. Case report. *J Neurosurg* 2005;102:540–2.
5. Sun BL, Wang LH, Yang T, *et al.* Lymphatic drainage system of the brain: a novel target for intervention of neurological diseases. *Prog Neurobiol* 2018;163–164:118–143.
6. Abbott NJ, Pizzo ME, Preston JE, Janigro D, Thorne RG. The role of brain barriers in fluid movement in the CNS: is there a 'glymphatic' system? *Acta Neuropathol* 2018;135:387–407.
7. Vertosick FT, Selker RG. Brain stem and spinal metastases of supratentorial glioblastoma multiforme: a clinical series. *Neurosurgery* 1990;27:516–21; discussion 521–2.
8. Comen E, Norton L, Massagué J. Clinical implications of cancer self-seeding. *Nat Rev Clin Oncol* 2011;8:369–77.
9. Chiang AC, Massagué J. Molecular basis of metastasis. *N Engl J Med* 2008;359:2814–23.
10. Li F, Tiede B, Massagué J, Kang Y. Beyond tumorigenesis: cancer stem cells in metastasis. *Cell Res* 2007;17:3–14.
11. Germano I, Swiss V, Casaccia P. Primary brain tumors, neural stem cell, and brain tumor cancer cells: where is the link? *Neuropharmacology* 2010;58:903–10.
12. Minn AJ, Gupta GP, Siegel PM, *et al.* Genes that mediate breast cancer metastasis to lung. *Nature* 2005;436:518–24.
13. Capper D, Jones DTW, Sill M, *et al.* DNA methylation-based classification of central nervous system tumours. *Nature* 2018;555:469–474.