Reminder of important clinical lesson

Diagnostic uncertainty around seizures in advanced malignancy

Demiana Lenzi Lewis-Hanna,¹ Gurjeet Pamma²¹GP, The Royal Wolverhampton Hospitals, Birmingham, UK;²Oncology Department, Russells Hall Hospital, Birmingham, UK

Correspondence to Dr Demiana Lenzi Lewis-Hanna, dlhanna@doctors.org.uk

Summary

A 70-year-old lady with a resected Dukes B colon cancer, receiving adjuvant capecitabine and bevacizumab chemotherapy was admitted with Hickman line sepsis. During her admission, she developed seizures and periods of unresponsiveness and was suspected to have brain metastases. She was started on high dose steroids and sodium valproate and appeared to respond to this treatment. However an MRI scan revealed that she did not have brain metastases but a rare neurological condition called reversible posterior leukoencephalopathy syndrome, which can be fatal if not treated but has a good prognosis if the cause is identified and treated.

BACKGROUND

Seizures in patients with a malignancy are almost always presumed to be due to brain metastases. However, this case highlights the importance of looking beyond the obvious and considering other causes. In this case, the cause of the seizures was a rare reversible neurological condition with serious consequences if not detected and treated but a good prognosis if detected and the cause corrected. This condition was reversible posterior leukoencephalopathy syndrome (RPLS), which is characterised by seizures, headaches and an altered mental state.¹ RPLS is diagnosed according to clinical and radiological features. It has a characteristic appearance on MRI and can result in haemorrhage and infarction if not detected.² It is associated with a number of clinical entities including eclampsia, renal disease, use of immunosuppressants and cytotoxic agents.² In this case report, RPLS occurs as a result of bevacizumab treatment and completely resolved after bevacizumab was stopped in the patient.

CASE PRESENTATION

A 70-year-old lady with a resected Dukes B cancer of the sigmoid colon and no metastasis, presented with rigors and general malaise. She was receiving adjuvant capecitabine and bevacizumab (avastin) chemotherapy via her Hickman line as part of the QUASAR-2 trial. On admission, her blood pressure was 112/63, pulse 130 per min, temperature 37.5°C and oxygen saturations were 97% on air. Examination was unremarkable and her bloods on admission were relatively unremarkable (table 1). She was treated for presumed line sepsis with intravenous antibiotics. The following day she developed a temperature of 38.3°C, a raised white cell count and raised C reactive protein (table 1). Blood cultures were positive for pseudomonas and subsequently her Hickman line was removed. She had two previous admissions for line sepsis over the last year.

Her medical history included mild angina, treated hypertension, a right bilobectomy for carcinoid tumour of the

lung and tinnitus. She stopped smoking 20 years previously and used to smoke 40 cigarettes a day. She drank one unit of alcohol per week.

One week later, she had periods of unresponsiveness and fit-like episodes which resolved spontaneously and she developed left-sided weakness.

She was thought to have cerebral metastases so an urgent CT head was requested and she was started on high dose dexamethasone and an anticonvulsant (sodium valproate). She responded well to the treatment and her weakness started to improve. The CT head revealed oedema in the right frontoparietal lobe hence implying the presence of metastases. To confirm the presence of brain metastases and enable radiotherapy to be planned an MRI head was arranged. Surprisingly, this did not reveal brain metastases but rather white matter changes in the right hemisphere consistent with RPLS.

INVESTIGATIONS

Table 1 shows her blood test results on the day of admission and the following day after she developed a temperature.

Table 1 Blood test results on the day of admission and the following day after the patient developed a temperature

Test	Blood results on admission	Blood results the following day
Sodium (mmol/l)	133	131
Potassium (mmol/l)	3.6	3.6
Urea (mmol/l)	6.5	5.6
Creatinine (μmol/l)	106	103
Calcium (mmol/l)	2.26	2.09
Phosphate (mmol/l)	0.73	0.67
C reactive protein (mg/l)	12	271
INR	1.2	1.7
Haemoglobin (g/dl)	12.2	9.1
White cell count ($\times 10^9/l$)	2.9	12.3
Platelets ($\times 10^9/l$)	170	160

INR, international normalised ratio.

Figure 1 Admission MRI: there is high signal in the subcortical white matter and the centrum ovale of the right frontal and parietal lobes. However, the cortex is spared.

Figure 2 Six weeks after withdrawal of bevacizumab. It demonstrates resolution of the white matter signal changes 6 weeks after withdrawal of bevacizumab.

A CT head done on the day she developed the first fit-like episode revealed oedema in the right frontoparietal lobe implying the presence of metastases.

The following day an MRI head was done which did not show any metastases, rather it showed high signal in the subcortical white matter and centrum semiovale of the right frontal and parietal lobe with sparing of the

cortex. The overall morphology and sparing of the cortex was against arterial infarction or cerebritis as an explanation for the white matter changes. There was no evidence suggesting venous infarction and the MRI findings pointed towards a chemotherapy related leukoencephalopathy on background small vessel ischaemic changes (figure 1). Metastases on MRI may show as ring-enhancing lesions with surrounding oedema. Lesions are isointense to mildly hypointense on T1-weighted images; they are hyperintense on T2-weighted images.³ Surrounding oedema is relatively hypointense on T1-weighted images; it is hyperintense on T2-weighted images.³

DIFFERENTIAL DIAGNOSIS

- ▶ CVA
- ▶ Seizure secondary to brain metastases
- ▶ Seizures provoked by metabolic derangement for example, malignant hypercalcaemia
- ▶ RPLS.

TREATMENT

The patient was treated with intravenous antibiotics for her pseudomonas Hickman line sepsis and was managed conservatively with regards to the RPLS. Her blood pressure was monitored carefully and controlled as this is another causative factor for RPLS.

OUTCOME AND FOLLOW-UP

Her treatment with bevacizumab was discontinued and a repeat MRI 6 weeks later (figure 2) showed resolution of the white matter changes. Her left-sided weakness resolved and she had no further seizures.

DISCUSSION

RPLS is a rare, reversible neurological condition that is diagnosed according to clinical and radiological features.¹ It has an acute to subacute onset and generally occurs in adults but has been reported occasionally in children.¹ Typical presenting features include seizures, headaches, altered mental state and visual disturbances.^{1 2} Although the pathogenesis remains unclear, it is frequently associated with a sudden increase in blood pressure. It is seen in patients with eclampsia, pre-eclampsia, renal failure, hypertensive encephalopathy and those taking immunosuppressants or cytotoxic agents.^{2 4} Previously reported cytotoxic chemotherapy agents associated with RPLS include 5-fluorouracil, cisplatin,⁵ gemcitabine^{6 7} and bevacizumab.⁸ Bevacizumab is a recombinant humanised monoclonal IgG1 antibody that binds and inhibits vascular endothelial growth factor.⁸ It is used in the treatment of metastatic bowel cancer as well as metastatic breast cancer and non-small-cell lung cancer.

The lesions in RPLS can be visualised on CT which classically shows bilateral areas of low attenuation in the posterior parietal and occipital white matter, although the grey matter can also occasionally be involved. However, MRI is the best imaging modality and T2-weighted images will demonstrate diffuse hyperintensity in the same distribution.^{2 4}

Although RPLS is a rapidly evolving condition, radiological and clinical findings are usually reversible within a few weeks after rectification of the precipitating event

or withdrawal of the causative agent. However failure to recognise and treat the syndrome can result in serious consequences such as permanent neurologic defects with progression to infarction, haemorrhage or death.²

RPLS has been reported with bevacizumab but is a very rare occurrence. There have been over 80 reports in the English literature that associate RPLS with various causes including chemotherapy agents and immunosuppressants.⁹

Learning points

- ▶ It is important to look beyond the obvious and carefully consider all possible causes for patient's symptoms.
- ▶ Not all patients with a malignancy who present with seizures have brain metastasis.
- ▶ RPLS is a rare, reversible neurological condition that is diagnosed according to clinical and radiological features and if undetected can result in serious consequences.
- ▶ Although the pathogenesis of RPLS remains unclear it is seen in patients with eclampsia, pre-eclampsia, renal failure, hypertensive encephalopathy and those taking immunosuppressants or cytotoxic agents.^{2 4}

Acknowledgements Russells Hall Hospital, Georgina Unit.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **Hinchey J**, Chaves C, Appignani B, *et al.* A reversible posterior leukoencephalopathy syndrome. *N Engl J Med* 1996;**334**:494–500.
2. **Kwon EJ**, Kim SW, Kim KK, *et al.* A case of gemcitabine and cisplatin associated posterior reversible encephalopathy syndrome. *Cancer Res Treat* 2009;**41**:53–5.
3. **Khosla A**. Brain metastasis imaging. Medscape. (Updated 2011 May 25) <http://emedicine.medscape.com/article/338239-overview#a21> (accessed 30 July 2011).
4. **Garg RK**. Posterior leukoencephalopathy syndrome. *Postgrad Med J* 2001;**77**:24–8.
5. **Kim GH**, Cho TH, Park JY, *et al.* Leukoencephalopathy associated with 5-fluorouracil and cisplatin therapy. *J Korean Neurosurg Soc* 1996;**25**:622–6.
6. **Rajasekhar A**, George TJ Jr. Gemcitabine-induced reversible posterior leukoencephalopathy syndrome: a case report and review of the literature. *Oncologist* 2007;**12**:1332–5.
7. **Russell MT**, Nassif AS, Cacayorin ED, *et al.* Gemcitabine-associated posterior reversible encephalopathy syndrome: MR imaging and MR spectroscopy findings. *Magn Reson Imaging* 2001;**19**:129–32.
8. **Ozcan C**, Wong SJ, Hari P. Reversible posterior leukoencephalopathy syndrome and bevacizumab. *N Engl J Med* 2006;**354**:981–2.
9. **Glusker P**, Recht L, Lane B. Reversible posterior leukoencephalopathy syndrome and bevacizumab. *N Engl J Med* 2006;**354**:980–1.

This pdf has been created automatically from the final edited text and images.

Copyright 2011 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit

<http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Lewis-Hanna DL, Pamma G. Diagnostic uncertainty around seizures in advanced malignancy. *BMJ Case Reports* 2011;10.1136/bcr.05.2011.4265, Published XXX

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow