CASE REPORT

Tumefactive demyelination presenting during bevacizumab treatment

Claire M Rice,^{1,2} David Rossiter,¹ Janev Fehmi,¹ James C Stevens,¹ Shelley A Renowden,³ Nicki Cohen,^{2,4} Clare Bailey,⁵ Neil J Scolding^{1,2}

¹Department of Neurology, North Bristol, NHS Trust Bristol, UK

²School of Clinical Sciences, University of Bristol, Bristol, UK

³Department of Neuroradiology, North Bristol, NHS Trust Bristol, UK

⁴Department of Neuropathology, North Bristol, NHS Trust Bristol, UK

⁵Bristol Eye Hospital, Lower Maudlin Street, Bristol, UK

Correspondence to

Dr Claire M Rice,
c.m.rice@bristol.ac.uk

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SUMMARY

We report the emergence of tumefactive demyelination during treatment with intravitreal bevacizumab (Avastin). This is of particular significance given that bevacizumab is currently being assessed as a potential treatment option for neuromyelitis optica, another demyelinating condition.

BACKGROUND

Bevacizumab is a humanised monoclonal antibody directed against the human 165-amino acid isoform of vascular endothelial growth factor A (VEGF-A) and inhibits angiogenesis. In addition to licensed indications for treatment of some malignancies, a clinical trial of bevacizumab as treatment for neuromyelitis optica (NMO) and NMO spectrum disorder (NMOSD) is in progress. We report emergence of tumefactive demyelination during treatment with intravitreal bevacizumab (Avastin).

CASE PRESENTATION

A 9-year-old girl presented with rapid onset of bilateral visual failure with optic disc swelling. At the posterior pole, bilateral and symmetrical changes were noted. On MRI, there was high signal in the optic nerves and lesions in the deep white matter consistent with either lacunar infarcts or demyelination. Cerebrospinal fluid (CSF) constituents were normal and oligoclonal bands were not detected. Following treatment with corticosteroids and immunoglobulin, visual acuity recovered to 6/9 in each eye. Subsequently, the abnormalities observed at the posterior poles were confirmed on ultrasound and CT to be consistent with choroidal osteomas. Visual-evoked potentials were abnormal but ultimately the changes were attributed to severe bilateral macular dysfunction.

At 20 years of age, the patient developed subfoveal choroidal neovascularisation in the right eye secondary to choroidal osteoma. Visual acuity deteriorated to 2/60. Loss of the P50 component on pattern electroretinography (ERG) suggested deteriorating macular function. Within a year, she developed a contralateral choroidal neovascular membrane, which was treated with systemic steroids and photodynamic treatment. Only hand movements could be detected on the right, but left-sided acuity improved to 6/12.

Intravitreal bevacizumab treatment (1.25 mg) for left-sided, recurrent choroidal neovascularisation was started when the patient was 26 years of age (figure 1). After the fourth treatment, she

developed mild, left upper limb pyramidal weakness and dysaesthesiae associated with left upper limb focal motor seizures and a secondary-generalised seizure.

INVESTIGATIONS

Screening for HIV, toxoplasmosis, cryptococcus and mycobacterial infection was negative. A 35 mm mass with irregular peripheral enhancement and associated oedema was noted in the right parietal lobe on brain MRI (figure 1). There was relatively little mass effect but a number of additional T2 hyperintense foci were seen in the subcortical and periventricular white matter. Cervical spine MR was normal. CSF analysis revealed 2 white cells/mm³, with elevated protein concentration (0.58 g/L, normal <0.49 g/L). An identical pattern of IgG bands was noted in serum and CSF. An EEG was consistent with a liability to partial onset seizures. CT imaging of the chest, abdomen and pelvis was unremarkable. Analysis of an image-guided brain biopsy demonstrated an infiltrate of T lymphocytes, plasma cells and foamy macrophages with extensive demyelination, gliosis and relative preservation of axons (figure 1).

TREATMENT

Anticonvulsant medication was instituted. Over 4 weeks, two courses of intravenous methylprednisolone (1 g daily for 3 days) had minimal effect. Resolution of neurological signs and radiological improvement followed plasmapheresis (8 exchanges) (figure 1).

OUTCOME AND FOLLOW-UP

There has been no evidence of new inflammatory activity either clinically or on serial MRI over a 2-year period.

DISCUSSION

Bevacizumab (Avastin) is a humanised monoclonal antibody directed against the human 165-amino acid isoform of VEGF-A, a member of the platelet derived growth factor/VEGF family of growth factors. VEGF-A acts on endothelial cells to promote angiogenesis, vasculogenesis and increased vascular permeability. VEGF inhibition is effective in the treatment of choroidal and retinal neovascularisation and impaired blood supply was the postulated mechanism underlying the emergence of retrobulbar optic neuritis in a patient with metastatic breast carcinoma treated with bevacizumab.¹

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Figure 1 Fundal images ((A) and (B)) at the time of presentation with seizures, and left upper limb symptoms showing bilateral choroidal osteomas and central macular fibrotic changes secondary to choroidal neovascularisation. MRI of the brain at presentation (C–F) and at 2 months post-treatment (G–J). Axial T2-weighted images (C, D, G and H), coronal fluid attenuated inversion recovery (E and I) and T1-weighted gadolinium enhanced coronal images (F and J). Cranial MRI at presentation demonstrated a right-sided parietal lesion with surrounding oedema, relatively little mass effect (C and E) and partial ring enhancement (F). There were a number of additional small white matter T2-hyperintense lesions in the subcortical (C and G) and deep white matter (D and H). Post-treatment, there was considerable reduction in the size and degree of enhancement of the right parietal lesion, with a small area of cavitation (G, I and J). Microscopic evidence of demyelination (K–N). Images are of adjacent sections of brain biopsy sample with grey–white matter interface in the lower left hand corner (line). Sections are stained for H&E, CD3, phosphorylated neurofilament (NF) and solochrome cyanine (SC). Scale bar=200 μ m. Histopathology demonstrated gliotic white matter with relative preservation of axons. The inflammatory infiltrate was largely perivascular (arrow) with a prominent small reactive T-cell population.

Reduced levels of VEGF-A are reported in CSF mononuclear cells of patients with multiple sclerosis (MS); reduced peripheral blood mononuclear cell levels of VEGF-A have been suggested as a marker of secondary progressive MS.² Production of VEGF-A by astrocytes disrupts the blood–brain barrier; while VEGF inhibition ameliorates disease in an animal model of MS.³ Furthermore, sera from patients with NMO reduce expression of tight junction proteins in culture and this has been attributed to upregulation of VEGF.⁴ Blockade of VEGF-A has therefore been proposed as a treatment strategy for demyelinating disease and a clinical trial of bevacizumab therapy in NMO and NMOSD is ongoing (NCT01777412). A single case of successful treatment of MS-associated uveitis with bevacizumab has been reported.⁵

A definite causal association between VEGF-A inhibition and central nervous system inflammatory demyelination cannot be confirmed in our patient, who may have a predisposition to demyelinating disease. However, the temporal relationship between institution of bevacizumab therapy and presentation with tumefactive demyelination is striking. The possibility of a causal relationship between the occurrence of tumefactive demyelination and use of fingolimod, a sphingosine 1-phosphate receptor modulator licensed for the treatment of relapsing-remitting MS, has been raised previously, and these cases illustrate how paradoxical effects of therapeutic agents may occur in clinical practice.^{6,7}

Our case highlights the need for caution among clinicians prescribing new biological therapies, particularly if there is a

predisposition to demyelinating disease, and serves as a useful reminder of the need for careful monitoring during and after treatment. New biological therapies may be less specific than anticipated and have unexpected effects in vivo. Furthermore, reporting of cases where serious adverse events have occurred is of importance given that low frequency events may not be detected in clinical trials.

Learning points

- ▶ Bevacizumab is an anti vascular endothelial growth factor A agent that inhibits vasculogenesis.
- ▶ Bevacizumab ameliorates an animal model of multiple sclerosis and clinical trials of its use for the treatment of neuromyelitis optica are in progress.
- ▶ We report the emergence of tumefactive demyelination during treatment with bevacizumab.
- ▶ We reiterate the importance of surveillance for low-frequency events associated with drug use.

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Competing interests None declared.

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