Systemic Inflammatory Reaction to Intravitreal Bevacizumab: A Case Report

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Research Article

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Abstract

Introduction

To present a case of systemic inflammatory reaction, with associated pleural and pericardial effusions, following intravitreal bevacizumab for retinal macroaneurysm.

Case presentation

A 73 year old female was commenced on monthly intravitreal bevacizumab injections for right eye macroaneurysm and associated macular oedema. Eight days following her third injection, the patient was admitted to hospital with a history of fever, rigors, arthralgia and vomiting. Admission blood tests demonstrated mild thrombocytopaenia and raised inflammatory markers. A CT chest revealed small pericardial and pleural effusions. The patient improved without treatment and was later discharged from hospital. As intravitreal bevacizumab treatment continued, the patient developed two further episodes of fever and vomiting, with both episodes occurring approximately nine days following each injection. The patient then underwent outpatient medical review by infectious disease and rheumatology specialists, at which time the recurrent episodes of systemic inflammation were diagnosed as secondary to intravitreal bevacizumab.

Conclusions

Though rare, patients can develop serious and potentially life-threatening systemic adverse effects from intravitreal anti-VEGF treatment. Ophthalmologists should always enquire about systemic side effects; in this way, adverse effects may be recognised sooner and a change or cessation of therapy considered.

Introduction

Systemic adverse effects from intravitreal anti-vascular endothelial growth factor (VEGF) treatment are rare [1]. However, monoclonal antibodies, as with other exogenous proteins, are recognised to provoke immuno-inflammatory reactions [2]. We present a case of systemic inflammatory reaction, with associated pleural and pericardial effusions, following intravitreal bevacizumab treatment for retinal macroaneurysm.

Case Presentation

A 73 year old female was referred to a medical retina clinic with an acute decline in vision in her right eye. The patient's ophthalmic history was significant for previous left branch retinal vein occlusion, hypertensive retinopathy, age-related macular degeneration and bilateral mild cataract. Her right eye best corrected visual acuity (BCVA) was recorded as 6/60. A macroaneurysm within the right superotemporal arcade was detected with significant surrounding haemorrhage and macular oedema (Figure 1). Following informed consent, the patient was commenced on a course of monthly 1.25mg intravitreal

bevacizumab injections to the right eye. The macular oedema responded to this anti-VEGF treatment with improvement in central foveal thickness from 479µm to 285µm following three injections, although her BCVA remained 6/60.

Eight days following her third bevacizumab injection, the patient was admitted to hospital with a three day history of fever, rigors, arthralgia and vomiting. Admission blood tests demonstrated mild thrombocytopaenia and CRP 22. Autoimmune screening was positive for lupus anticoagulant and borderline positive ANA at 1:320. Routine and atypical infectious disease screens were negative. A CT chest demonstrated small pericardial and pleural effusions with mediastinal lymphadenopathy. The patient was discharged after four days with no further episodes of fever recorded whilst in hospital. No antibiotic or steroid therapy was initiated during her stay.

Following two additional bevacizumab injections and right eye cataract surgery, the patient's right BCVA improved to 6/24. However, two further episodes of fever and vomiting were noted to occur around nine days following both injections. The patient underwent outpatient review by infectious disease and rheumatology specialists. Her recurrent episodes of systemic inflammation and fever were diagnosed as secondary to intravitreal bevacizumab. A change in intravitreal treatment was therefore recommended. At a subsequent ophthalmology appointment, the patient was diagnosed with branch retinal vein occlusion in the same eye and a course of intravitreal aflibercept was initiated. No systemic inflammatory reactions have been noted following aflibercept injections and right BCVA has improved to 6/9.

Conclusions

As a focal dilatation of a retinal arteriole, macroaneurysms typically occur in female hypertensive patients [3]. Observation is appropriate in asymptomatic patients. However, patients may present with an acute deterioration in vision secondary to macular oedema or vitreous haemorrhage [3]. Intravitreal bevacizumab has been shown to improve macroaneurysm-associated macular oedema [4].

Bevacizumab, commonly referred to by its trade name Avastin, is often prescribed off-license in the United Kingdom for macular oedema or neovascularisation, in patients who do not meet funding criteria for aflibercept or ranibizumab. Although anti-VEGF drugs are detectable in the systemic circulation following intravitreal injection, systemic side effects are rare [1, 5]. Intravitreal anti-VEGF therapy has been linked to non-ocular haemorrhage, arterial thromboembolic events and systemic infections [1]. The systemic safety profiles of bevacizumab, ranibizumab and aflibercept, the three most commonly prescribed anti-VEGF agents, are not considered to be significantly different [1].

In a twelve-month case series of 1,173 patients receiving intravitreal bevacizumab, systemic adverse events were reported in 1.5% of patients. These included acute elevations in blood pressure (0.59%), cerebrovascular accidents (0.5%), myocardial infarctions (0.4%) and death (0.4%) [6].

Bevacizumab is a humanized monoclonal antibody that inhibits vascular endothelial growth factor A (VEGF-A) [3]. Other monoclonal antibody therapies are associated with systemic inflammation; this is the

result of a hypersensitivity drug reaction and referred to as serum sickness [2]. In these type III hypersensitivity reactions, antibodies develop in response to an antigen, forming antigen-antibody or immune complexes [2]. If the mononuclear phagocyte system is saturated by the immune complex load, excess complexes can form and deposit throughout the body, triggering an inflammatory response and activating the complement system. In this case, although the mechanism of systemic inflammation is likely the result of a bevacizumab hypersensitivity reaction, the patient did not meet criteria for a diagnosis of serum sickness.

Following a change in anti-VEGF therapy from bevacizumab to aflibercept, the patient has not experienced any further inflammatory episodes. Aflibercept is a recombinant fusion protein that acts as a decoy receptor for VEGF-A and VEGF-B, as well as binding to placental growth factor [3]. Its different molecular composition to bevacizumab may explain why the patient has not developed an immune response to this drug.

Though rare, this case serves as a reminder that patients can develop serious and potentially life-threatening systemic adverse effects from intravitreal anti-VEGF treatment. Ophthalmologists should enquire about systemic side effects in patients undergoing anti-VEGF injections. In this way, adverse effects may be recognised sooner and a change or cessation of therapy considered.

Abbreviations

Anti-VEGF - anti-vascular endothelial growth factor; BCVA - best corrected visual acuity

Declarations

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The authors did not receive any funding in relation to this case report.

Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

Not applicable.

Consent for publication

The patient presented in this case report provided written consent for publication.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the study.

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Authors' contributions

SB collected the case data and drafted the manuscript with oversight and input from RS and RA. All authors read and approved the final manuscript.

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Figures

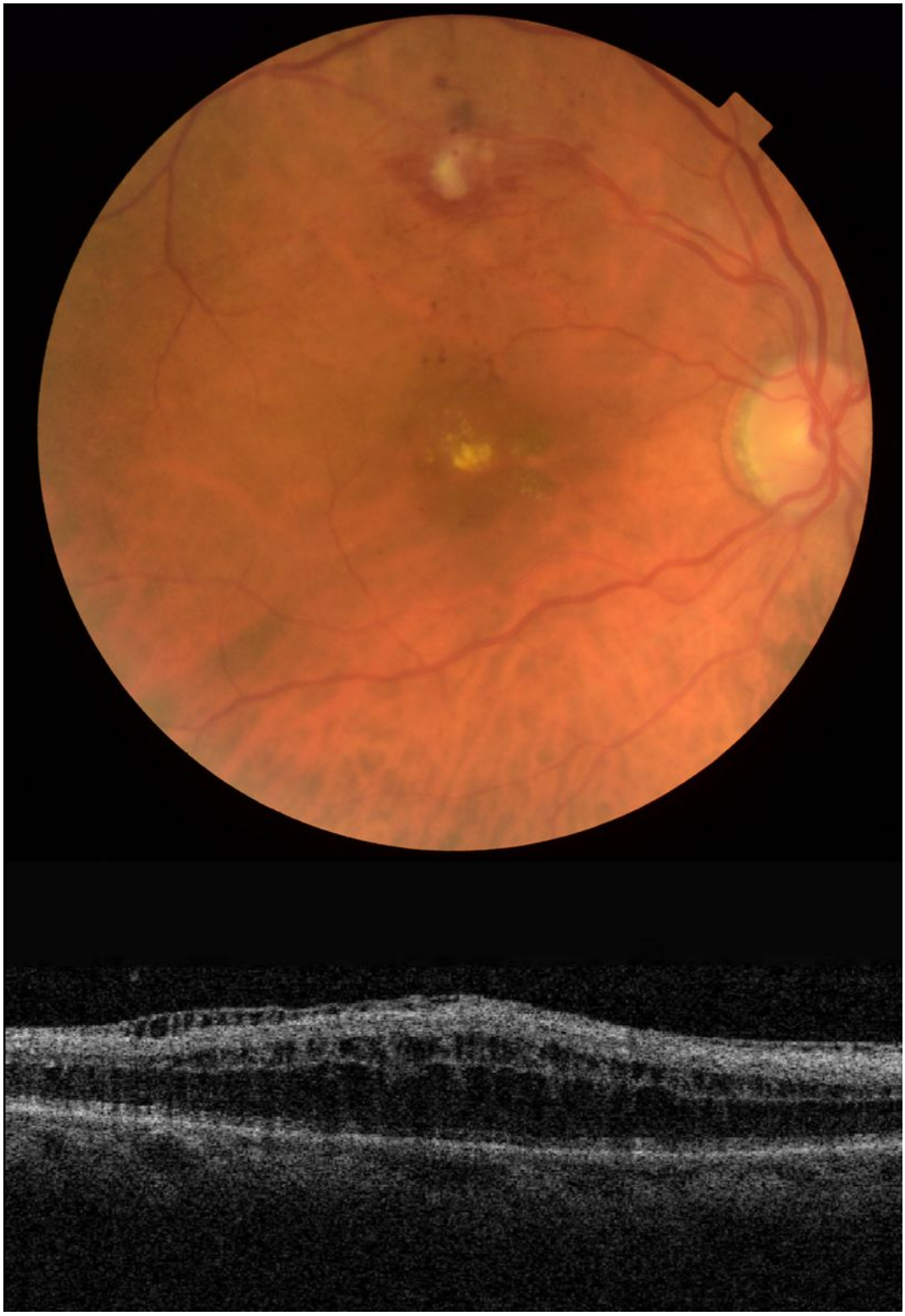

Figure 1

Right eye fundus photo and OCT macula at time of macroaneurysm diagnosis

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