Unexpected outcome (positive or negative) including adverse drug reactions

Diffuse alveolar haemorrhage may be associated with intravitreal injection of bevacizumab in a patient with systemic risk factors

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Summary

The authors present a rare case where acute respiratory failure occurred after the intravitreal bevacizumab injection for a branch retinal vein occlusion. Chest CT scan showed ground-glass opacity in the bilateral lung fields. The finding of bronchoalveolar lavage fluid revealed alveolar haemorrhage. Corticosteroid therapy resulted in a rapid improvement of respiratory failure. This report suggests that intravitreal injection of bevacizumab may be associated with diffuse alveolar haemorrhage and acute lung injury.

BACKGROUND

Vascular endothelial growth factor (VEGF), an endothelial cell-specific mitogen, is the major regulator of angiogenesis in normal and malignant tissue.¹ Increased expression of VEGF has been found in most tumours in humans, including non-small-cell lung cancer (NSCLC), and also in branch retinal vein occlusion (BRVO), a common retinal vascular disorder seen in the elderly.²⁻³ Based on these findings, the injection of bevacizumab, a humanised anti-VEGF monoclonal antibody, into the eye of a patient with central retinal vein occlusion has been applied. The efficacy and safety of this treatment have been supported by several lines of evidence.⁴⁻⁶ On the other hand, in other clinical trials of bevacizumab, hypertension, proteinuria and bleeding have been reported, which are also minor in severity.⁷ Of much great concern, however, is the occurrence of life-threatening pulmonary haemorrhage associated with bevacizumab, particularly in patients with squamous-cell lung cancer.⁹ Here, we present a patient who developed diffuse alveolar haemorrhage (DAH) and severe respiratory failure after intravitreal injection of bevacizumab for the treatment of BRVO.

CASE PRESENTATION

An 86-year-old man was admitted to our hospital with rapidly progressive dyspnoea. One day prior to the admission, he had received the second course of intravitreal injection of 1.25 mg bevacizumab into his left eye for BRVO after 3 months from the first course. There had been no episode of aspiration since he had received subtotal gastrectomy for gastric cancer when he was 61. He quit smoking 26 years ago with a smoking history of 62 pack-years. He had no history of drug allergy. He had been a farmer.

The vital signs on admission were body temperature, 37.9 °C; pulse rate, 109/min; respiratory rate, 26/min; and blood pressure, 144/96 mm Hg. Physical examination revealed bilateral wheezing without other abnormal

findings. Partial arterial pressure of oxygen was 57.8 mm Hg on 10l/min oxygen mask support.

INVESTIGATIONS

Chest x-ray showed bilateral reticular opacities at both middle and lower lung fields. Chest CT scan showed bilateral peribronchovascular distribution of ground-glass opacities (figure 1). Echocardiogram revealed normal cardiac functions. Laboratory findings were white blood cell count of $4.4 \times 10^9/l$, haemoglobin of 123 g/l, haematocrit of 40.1% and platelet count of $227 \times 10^9/l$. C reactive protein, brain natriuretic peptide, Krebs von den Lunge-6, surfactant protein-D, coagulation time and D-dimer were within normal limits. Serological tests for connective tissue diseases, including antinuclear antibody, perinuclear antineutrophil cytoplasmic antibodies (ANCA), cytoplasmic ANCA and antiglomerular basement membrane antibodies, were also within normal limits. Other biochemical parameters, including urine analyses, were within normal limits.

Bronchoscopy and bronchoalveolar lavage (BAL) were performed. BAL fluid (BALF) obtained from the right medial segmental bronchus appeared haemorrhagic and indeed many red blood cells were found in the fluid. Differential cell count of BALF revealed neutrophilic inflammation (43% of the volume was restored, a total cell count of $54.7 \times 10^5/l$, 85% neutrophils, 0% eosinophils, 2% lymphocytes, 13% macrophages). Cytologic examination did not show any malignant cells, viral cytopathic changes or fungal elements in BALF. Culture of BALF did not show any remarkable bacteria, mycobacterial or fungal pathogens. *Pneumocystis jiroveci* was not detected by PCR in the BALF. Blood cultures were also negative.

DIFFERENTIAL DIAGNOSIS

DAH may be caused by a variety of disorders including congestive heart failure, infection, thromboembolism, coagulopathy, idiopathic pulmonary haemosiderosis,

Figure 1 CT scan showing bilateral ground-glass opacities on admission.

Figure 2 CT scan showing the improvement of ground-glass opacities on the fifth day of the admission after corticosteroid therapy.

collagen vascular disease and vasculitis (including Wegener's granulomatosis, microscopic polyangiitis and Goodpasture syndrome).¹⁰ A disintegration of the alveolar-capillary barrier can be the underlying mechanism of DAH.¹¹

We considered this case as drug-induced DAH because bloody BAL aliquots were obtained and all the other differential diseases causing DAH were excluded by the investigation. The development of DAH after administration

of bevacizumab twice implied that bevacizumab was the most suspicious drug.

TREATMENT

The patient required mechanical ventilation with intubation on admission because of his severe respiratory condition. Intravenous methylprednisolone 1000 mg/body daily was given for three days, and this was followed by tapering of the dose of oral prednisolone.

OUTCOME AND FOLLOW-UP

The treatment was followed by significant clinical improvement (figure 2), which allowed us to extubate him within five days after the intubation. He was discharged 3 weeks after the admission and remains asymptomatic after the cessation of prednisolone.

DISCUSSION

The underlying mechanism of bevacizumab-induced lung injury is still poorly understood. Increasing evidence suggests that VEGF has a key role in the pathogenesis of acute lung injury.^{12 13} VEGF not only stimulates endothelial cell proliferation, but also promotes endothelial survival and helps maintain vascular integrity. Anti-VEGF therapy could thereby diminish the regenerative capacity of endothelial cells and cause defects that expose pro-coagulant phospholipids on the luminal plasma membrane or underlying matrix, leading to thrombosis or haemorrhage.¹⁴

In this case, bevacizumab was administered as a single agent unlike the previously reported case of acute lung injury associated with docetaxel and bevacizumab in the treatment for breast cancer.¹⁵ There have been no reported cases of acute lung injury or DAH associated with intravitreal injection of bevacizumab.

Interestingly, the pulmonary toxicity in this case may be caused by intravitreal injection of bevacizumab. Indeed, pharmacological study in a macaque model revealed that bevacizumab was detected in the serum after 1.25 mg bevacizumab intravitreal injection but its concentration was much lower than the reported concentration leading to systemic toxicity.¹⁶

Although risk factors that might predict the development of DAH have not been identified, older age and cigarette smoking are known as risk factors for the development of acute lung injury or acute respiratory distress syndrome.¹⁷ It should also be kept in mind that our patient had similar clinical findings in that he was a former cigarette smoker and extremely old. The patient condition might explain why intravitreal injection of bevacizumab, even though at lower serum concentration of bevacizumab in its use, could lead to the development of DAH and acute lung injury.

On the other hand, most cases of DAH are immunologically mediated by vasculitis or idiosyncratic drug reaction, which also causes a disintegration of alveolar

capillary barrier.¹⁹ In such cases, immunosuppressive therapy including corticosteroid may have a benefit. Our patient demonstrated DAH with the second course of 1.25 mg bevacizumab intravitreal injection and improved rapidly with corticosteroid therapy, which supports the notion of idiosyncratic drug reaction.

Although it might be a rare case, physicians should be aware that corticosteroid therapy is a therapeutic option if DAH was confirmed by BAL in patients with life-threatening respiratory failure after the administration of bevacizumab, irrespective of the route of administration.

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Competing interests None.

Patient consent Obtained.

REFERENCES

1. Ferrara N. The role of vascular endothelial growth factor in pathological angiogenesis. *Breast Cancer Res Treat* 1995;**36**:127–37.
2. Seto T, Higashiyama M, Funai H, et al. Prognostic value of expression of vascular endothelial growth factor and its flt-1 and KDR receptors in stage I non-small-cell lung cancer. *Lung Cancer* 2006;**53**:91–6.
3. Noma H, Minamoto A, Funatsu H, et al. Intravitreal levels of vascular endothelial growth factor and interleukin-6 are correlated with macular edema in branch retinal vein occlusion. *Graefes Arch Clin Exp Ophthalmol* 2006;**244**:309–15.
4. Funk M, Kriechbaum K, Prager F, et al. Intraocular concentrations of growth factors and cytokines in retinal vein occlusion and the effect of therapy with bevacizumab. *Invest Ophthalmol Vis Sci* 2009;**50**:1025–32.
5. Rosenfeld PJ, Fung AE, Puliafito CA. Optical coherence tomography findings after an intravitreal injection of bevacizumab (avastin) for macular edema from central retinal vein occlusion. *Ophthalmic Surg Lasers Imaging* 2005;**36**:336–9.
6. Gregori NZ, Rattat GH, Rosenfeld PJ, et al. Safety and efficacy of intravitreal bevacizumab (avastin) for the management of branch and hemiretinal vein occlusion. *Retina (Philadelphia, Pa)* 2009;**29**:913–25.
7. Gordon MS, Margolin K, Talpaz M, et al. Phase I safety and pharmacokinetic study of recombinant human anti-vascular endothelial growth factor in patients with advanced cancer. *J Clin Oncol* 2001;**19**:843–50.
8. Yang JC, Haworth L, Sherry RM, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med* 2003;**349**:427–34.
9. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 2004;**22**:2184–91.
10. Green RJ, Ruoss SJ, Kraft SA, et al. Pulmonary capillaritis and alveolar hemorrhage. Update on diagnosis and management. *Chest* 1996;**110**:1305–16.
11. Ioachimescu OC, Stoller JK. Diffuse alveolar hemorrhage: diagnosing it and finding the cause. *Cleve Clin J Med* 2008;**75**:258,60,64–5 passim.
12. Medford AR, Millar AB. Vascular endothelial growth factor (VEGF) in acute lung injury (ALI) and acute respiratory distress syndrome (ARDS): paradox or paradigm? *Thorax* 2006;**61**:621–6.
13. Abadie Y, Bregeon F, Papazian L, et al. Decreased VEGF concentration in lung tissue and vascular injury during ARDS. *Eur Respir J* 2005;**25**:139–46.
14. Kilickap S, Abali H, Celik I. Bevacizumab, bleeding, thrombosis, and warfarin. *J Clin Oncol* 2003;**21**:3542; author reply 3543.
15. Prat A, Martinez P, Serrano C, et al. Acute lung injury associated with docetaxel and bevacizumab. *Clin Oncol (R Coll Radiol)* 2007;**19**:803–5.
16. Miyake T, Sawada O, Kakinoki M, et al. Pharmacokinetics of bevacizumab and its effect on vascular endothelial growth factor after intravitreal injection of bevacizumab in macaque eyes. *Invest Ophthalmol Vis Sci* 2010;**51**:1606–8.
17. Iribarren C, Jacobs DR Jr, Sidney S, et al. Cigarette smoking, alcohol consumption, and risk of ARDS: a 15-year cohort study in a managed care setting. *Chest* 2000;**117**:163–8.
18. Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. *N Engl J Med* 2005;**353**:1685–93.
19. Rabe C, Appenrodt B, Hoff C, et al. Severe respiratory failure due to diffuse alveolar hemorrhage: clinical characteristics and outcome of intensive care. *J Crit Care* 2010;**25**:230–5.

Learning points

- This case report called our attention to the fact that the intravitreal injection of bevacizumab may be associated with DAH and acute lung injury.
- Older age and smoking might be systemic risk factors for DAH and acute lung injury in the use of bevacizumab.
- We recommend that early bronchoscopy with bronchoalveolar lavage should be performed so as to confirm the diagnosis.
- Because of the life-threatening side effects of bevacizumab-induced DAH, prompt initiation of corticosteroid therapy appears to confer benefit when the condition is suspected.

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