Clinical Case Report

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Maculopapular rash after intravitreal injection of an antivascular endothelial growth factor, aflibercept, for treating age-related macular degeneration

A case report

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Abstract

Rationale: Aflibercept, an anti-vascular endothelial growth factor (VEGF) drug, is used for treatment of colon cancer as well as retinal diseases, including wet age-related macular degeneration (AMD). It is injected into the vitreous cavity of eyes for treatment of AMD. Although vascular suppression—including cardiovascular events—and local infection related to the injection procedure are well-known potential adverse events, pathological immune responses after intravitreal aflibercept (IVA) injection have not been described.

Patient concerns: A 60-year-old Japanese man diagnosed with polypoidal choroidal vasculopathy (PCV), a subtype of wet AMD, was treated by anti-VEGF injection. Ten hours after the last IVA injection, he presented with systemic erythema with itching.

Diagnoses: On the basis of the palpable erythema and papules observed on the trunk and extremities, along with redness of the pharynx, the patient was diagnosed with maculopapular-type drug eruption. The findings of biopsy of erythematous skin on the back revealed lymphocyte infiltration and telangiectasia in the upper dermis, thus confirming the diagnosis.

Interventions: The patient was administered 30 mg prednisolone to resolve the immunoreaction.

Outcomes: With this treatment, the eruption turned brown, and the pharyngeal lesion and itching were resolved, and the maculopapular rash after intravitreal IVA was resolved.

Lessons: This case illustrates the importance of medical staff being aware of aflibercept—a widely used anti-VEGF drug in various fields, including retinal diseases—as a potential cause of drug allergy.

Abbreviations: AMD = age-related macular degeneration, BCVA = best-corrected visual acuity, IVA = intravitreal aflibercept, PDT = photodynamic therapy, VEGF = vascular endothelial growth factor.

Keywords: age-related macular degeneration, anti-VEGF drug, maculopapular rash

1. Introduction

Age-related macular degeneration (AMD) is a leading cause of blindness worldwide.[1] Wet AMD results in vision loss due to exudative changes caused by pathological neovascularization (choroidal neovascularization) beneath the macula. Recent advances in medical science have helped develop 3 approved antivascular endothelial growth factor (VEGF) drugs for the treatment of wet AMD – pegaptanib,[2] ranibizumab,[3] and aflibercept.[4,5] In addition to these 3 approved drugs, bevacizumab,[6] an off-label drug, is being used for intraocular injection into the vitreous cavity of eyes. Since patients with wet AMD experience remission and recurrence, these drugs are injected repeatedly at intervals of over a month. Aflibercept is the latest drug approved for the treatment of wet AMD. It is a recombinant fusion protein comprising the VEGF-binding portions of human VEGF receptors (VEGFRs) 1 and 2 and the Fc portion of human immunoglobulin G1. It binds not only to VEGF-A, but also to other VEGF family proteins, including VEGF-B and placental growth factor (PlGF).[7] It is also used for treating colon cancer. For treatment of AMD, aflibercept is injected into the vitreous cavity of the eye. Although it is effective for the treatment of choroidal neovascularization and AMD-associated exudative changes in the eye, suppression of vascular endothelial growth and permeability by targeting VEGF might also result in suppression of normal vascular-tissue maintenance. Consequently, cardiovascular events, mucocutaneous hemorrhage, and delayed or poor wound healing have been reported as potential systemic side effects of anti-VEGF treatment.[8] On the other hand, there are few reports of adverse events related to abnormal

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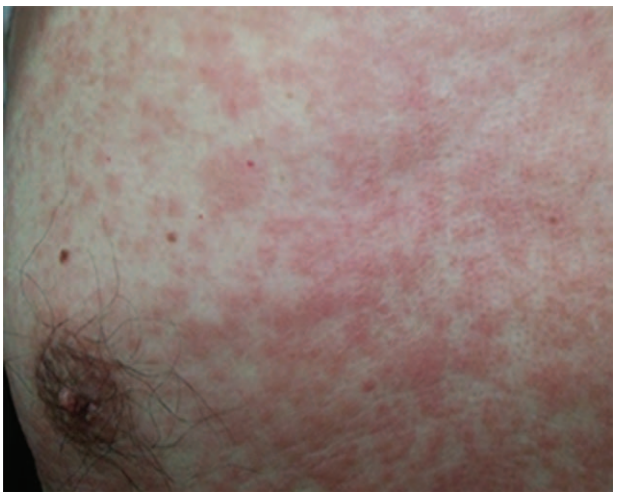

Figure 1. Maculopapular rash on the chest induced by intravitreal aflibercept injection.

immune responses upon intravitreal injection of anti-VEGF drugs. Here, we report the 1st-ever case of maculopapular rash after intravitreal aflibercept (IVA) injection for wet AMD.

2. Case presentation

This case report followed the tenets of the Declaration of Helsinki, was retrospectively approved by the Ethics Committee of Keio University School of Medicine (No. 2010002), and was registered with UMIN-CTR (UMIN000007649).

We report a case of a 60-year-old Japanese male office worker who presented with a maculopapular rash (Fig. 1) after IVA treatment for polypoidal choroidal vasculopathy, a subtype of wet AMD. Following diagnosis of polypoidal choroidal vasculopathy (Fig. 2A, B) in June 2012 at the Medical Retina Division Clinic, Department of Ophthalmology, Keio University Hospital, Tokyo, Japan, his left eye had been treated with 11 injections of 0.5 mg ranibizumab and 23 injections of 2 mg aflibercept, per requirement. At the first visit, the patient exhibited subretinal fluid beneath the macula (Fig. 2C) and a best-corrected visual acuity (BCVA) of 1.0 in decimal units (logarithm of the minimum angle of resolution [logMAR], 0). After several recurrences, the BCVA was still 1.0 in decimal units (logMAR, 0) before the 24th IVA injection (Fig. 2D). The patient had received treatment for hypertension and hyperuricemia during this period.

In April 2016, the patient returned to the hospital 10 hours after the 24th IVA injection with a complaint of systemic erythema with itching (Fig. 1). He presented with maculopapular-type drug eruption on the trunk and extremities, along with redness of the pharynx. The results of laboratory analysis revealed a leukocyte count of 8300/μL (lymphocytes, 23.6%; eosinophils, 4.2%) and C-reactive protein concentration of 0.04 mg/dL. The diagnosis was confirmed as drug-induced maculopapular rash by biopsy of erythematous skin on the back at the Department of Dermatology, Keio University Hospital, which revealed lymphocyte infiltration and telangiectasia in the upper dermis (Fig. 3). The patient was recommended to undergo the prick test; however, since he did not consent to the procedure, the test was not performed. Differential diagnosis included acute viral rash; however, there were no signs of viral infection. Despite

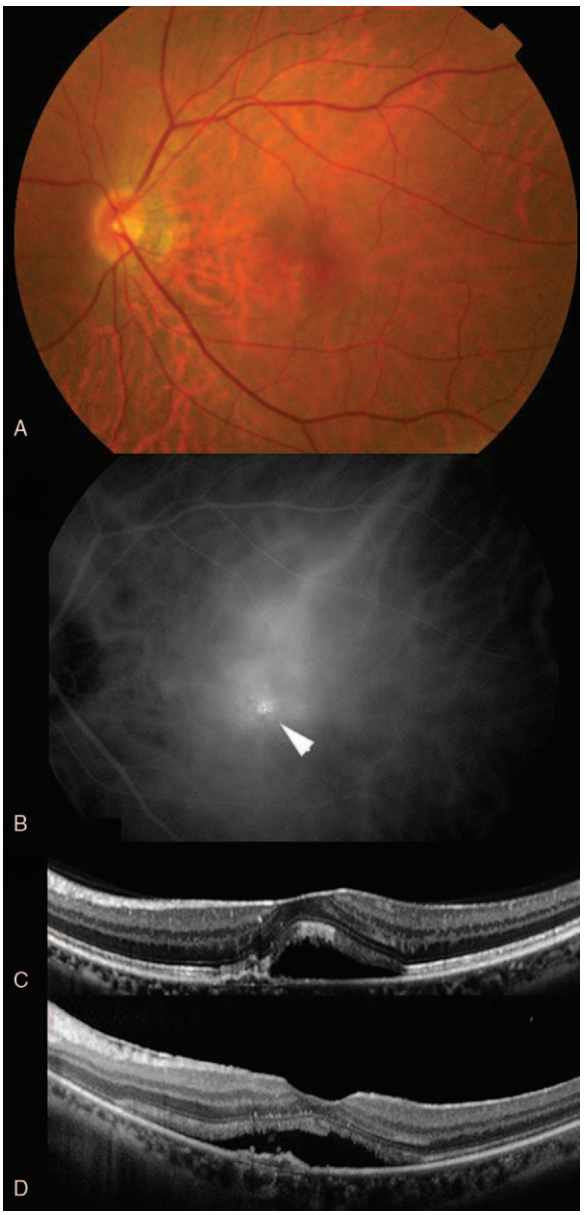

Figure 2. Fundus photographs and ICGA images acquired at the first visit and before the 24th intravitreal aflibercept injection. (A, B) Fundus photography and ICGA findings at the first visit demonstrated a polyp lesion corresponding to PCV, a subtype of AMD (arrow in B). (C, D) Optical coherence tomography images acquired at the first visit (C) and before the 24th intravitreal aflibercept injection (D). Exudative retinal detachment, observed at the first visit (C), was resolved after treatment (D). AMD = age-related macular degeneration, ICGA = indocyanine green angiography, PCV = polypoidal choroidal vasculopathy.

treatment with fexofenadine, an antihistamine, and betamethasone ointment for 2 days, the eruption increased, proving the treatment to be ineffective. The patient was then administered 30 mg prednisolone per day for a week to resolve the immunoreaction. With this treatment, the eruption turned brown, and the pharyngeal lesion and itching were resolved.

Exudative changes in the left eye regressed after the IVA injection, but recurred in 2 months (Fig. 4A–C). To avoid a similar event this time, the patient was not administered anti-VEGF drugs; instead, he was treated with photodynamic therapy (PDT), a selective vaso-occlusive treatment involving intravenous injection of verteporfin, a photosensitizing prodrug, followed by

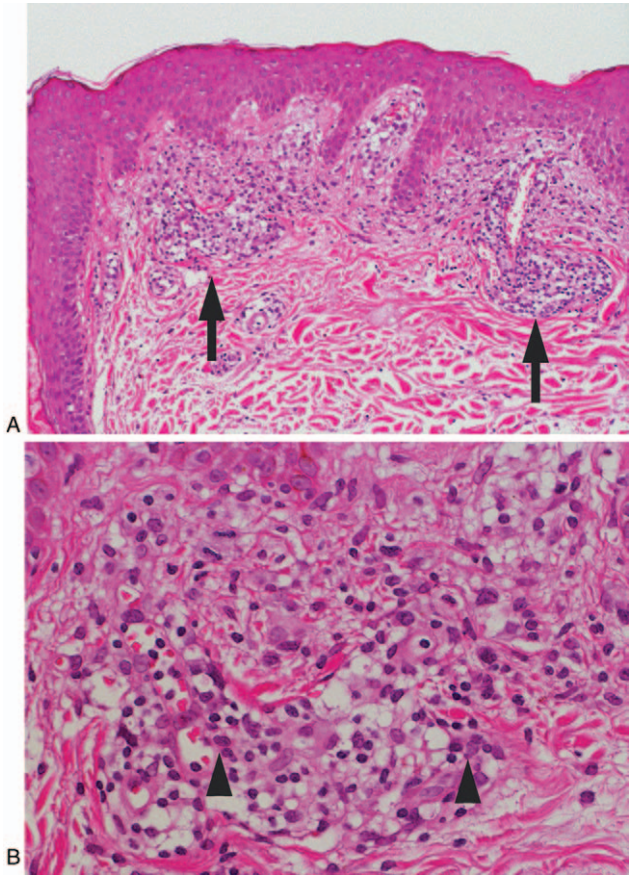

Figure 3. Histological findings of erythematous skin on the back. (A) Focal lymphocyte infiltration (arrows) and telangiectasia in the upper dermis. (B) At higher magnification, lymphocytes (arrowheads) are visible around the capillaries.

nonthermal laser light irradiation of the lesion. Upon PDT, the exudative change resolved, and the BCVA remained constant (Fig. 4D).

3. Discussion

The present case is the first report of type IV allergic reaction after IVA injection for the treatment of AMD. A case of cutaneous lupus erythematosus 6 weeks after intravitreal injection of bevacizumab, an off-label anti-VEGF drug for eyes,[9] and another case of acute exanthematous pustulosis 4 days after intravitreal injection of ranibizumab,[10] another anti-VEGF drug, have been previously reported. In clinical trials of aflibercept for wet AMD, VIEW 1/2, the incidences of skin and subcutaneous tissue disorders – which might involve systemic allergic responses – were reported to be 0.3% to 0.7%, although the details are unclear. According to the US Pharmacy Benefits Management Drug Monograph and US National Library of Medicine, incidences of immunoreactivity toward ranibizumab at baseline and after 1 to 2 years of treatment are 0% to 3% and 1% to 6%, respectively, while those toward aflibercept range from 1% to 3% in both cases. Interestingly, VEGFA–VEGFR pathway blockade has been shown to inhibit regulatory T-cell proliferation.[11] Severity of drug eruption is related to the decrease in immunosuppressive regulatory T cells.[12] Thus, consecutive VEGF blockade by repeated anti-VEGF administration might have promoted the immune reaction and contributed to the relatively early onset of drug eruption after the last IVA injection in the present case.

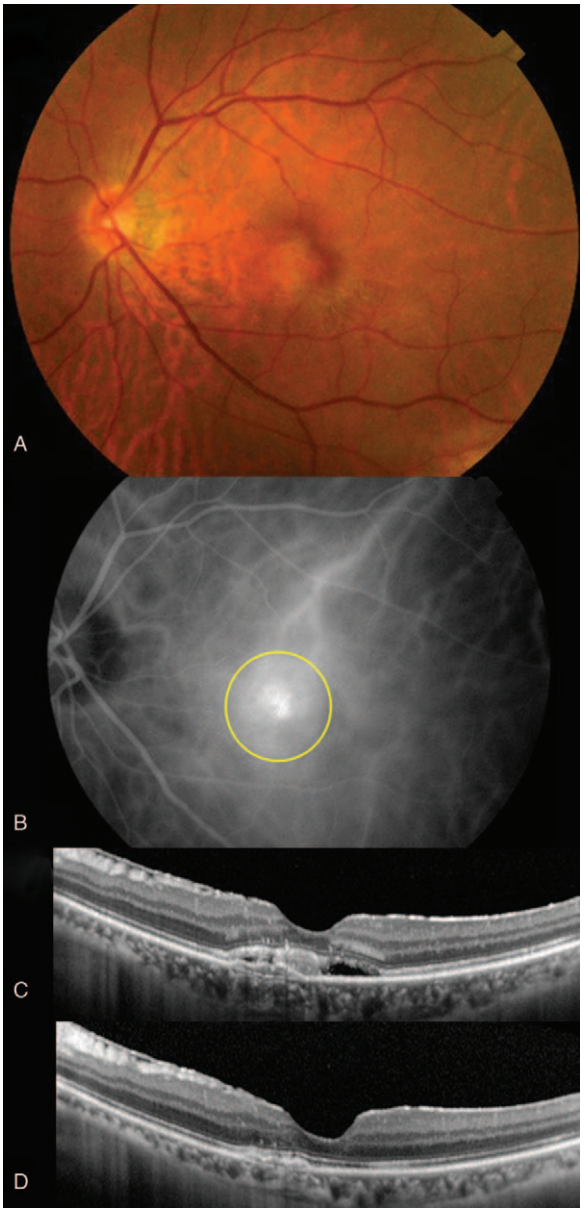

Figure 4. Fundus photograph and ICGA images acquired before and after PDT. (A, B) Fundus photography and ICGA findings recorded upon recurrence after the 24th intravitreal aflibercept injection. Indocyanine green leakage demonstrated the polyp and associated exudative changes; nonthermal laser irradiation was administered to the region (circle in B) under ICGA guidance. (C, D) Optical coherence tomography images acquired before (C) and 3 months after (D) PDT. Retinal detachment (C) was resolved by PDT (D). ICGA = indocyanine green angiography, PDT = photodynamic therapy.

To avoid the least possibility that the patient had gained immunoreactivity to ranibizumab as well – considering his possible hyperimmunosensitivity and history of ranibizumab use – ranibizumab therapy was not considered for further treatment, although anti-VEGF therapy is the 1st-line treatment for AMD worldwide. Instead, the patient was administered PDT, which resolved the exudative change. Although the patient received alcohol sterilization, local anesthetics, and mydriatic agents during PDT as well as at the last IVA injection, these factors did

not cause eruption at the time of PDT, which supports the idea that the eruption was caused by aflibercept. This idea is consistent with previous reports that other peptide drugs, such as monoclonal antibodies, are immunogenic.[13] However, it cannot be excluded that some of the drug constituents might have been responsible for the immunoreaction.

The EVEREST study, a clinical study on PDT, reported higher rates of polyp regression among patients treated by PDT than among patients who received ranibizumab monotherapy,[14] which also supported our decision to administer PDT in the present case. Although the recent trend is to avoid PDT for the treatment of AMD, PDT may be applicable in patients with suspected anti-VEGF drug allergy.

Aflibercept has been approved for the treatment of metastatic colorectal cancer along with FOLFIRI therapy in patients who exhibit resistance to or progression after oxaliplatin therapy.[15] In the tumor microenvironment, VEGFR-1 positive inflammatory cells play a crucial role in tumor outgrowth, regrowth, and metastatic dissemination. However, targeting of the PlGF–-VEGFR-1 axis by aflibercept can inhibit immune cell recruitment and metastatic progression.[16] In cases where patients with aflibercept allergy suffering from colon cancer – or vice versa – have a treatment plan involving the same drug, medical staff of both departments should carefully evaluate the medical history of the patients.

In conclusion, aflibercept, a widely used recombinant fusion protein targeting the VEGF family, exhibits good efficacy and tolerance in clinical trials for AMD. The present case is the first report of systemic adverse events caused by abnormal immune reaction against intraocularly administered aflibercept. Although the adverse reaction in the present case was confined to a rash, it could also involve long-term suppression of VEGF activity and consequences of the same on the immune system. This case illustrates the importance of medical staff in various fields being aware of local administration of aflibercept as a potential cause of maculopapular rash, a systemic adverse event which could lead to life-threatening conditions.

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