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Case Report

Exacerbation of Diabetic Retinopathy following Hypoxia-Inducible Factor-Prolyl Hydroxylase Inhibitor Administration: A Case Report

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Keywords
Hypoxia-inducible factor-prolyl hydroxylase inhibitor · Vascular endothelial growth factor · Diabetic retinopathy · Renal anemia

Abstract
Introduction: Hypoxia-inducible factor-prolyl hydroxylase (HIF-PH) inhibitors, used in the treatment of renal anemia, hold the potential to increase the production of vascular endothelial growth factors. Therefore, HIF-PH inhibitors may exacerbate retinal hemorrhage in diseases such as diabetic retinopathy. Here, we present a case involving the administration of an HIF-PH inhibitor, resulting in the exacerbation of retinal hemorrhage in a patient with diabetic retinopathy. ***Case Presentation:*** A 32-year-old man with diabetes mellitus and renal anemia caused by diabetic nephropathy was referred to our department for ophthalmic examination, revealing diabetic retinopathy with scattered retinal hemorrhages, exudates, and diabetic maculopathy in both eyes. Darbepoetin alfa was initially administered and switched to the HIF-PH inhibitor roxadustat on day 74. By day 88, fresh retinal hemorrhage was observed in the right eye. On day 132, the retinal hemorrhage had further worsened, with new preretinal hemorrhage in both eyes. Roxadustat was discontinued, replaced with darbepoetin alfa, resulting in retinal hemorrhage improvement by day 181 (49 days post-roxadustat cessation). On day 201, fundus hemorrhage further improved, optical coherence tomography showed no macular edema or subretinal fluid, and the retina was thinning. Fluorescein angiography showed neovascular vessels, active fluorescein leakage, and extensive avascular areas in both eyes, prompting pan-retinal photocoagulation. Visual acuity remained stable throughout treatment. ***Conclusion:*** Patients with advanced diabetic

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retinopathy taking HIF-PH inhibitors should be aware of retinal hemorrhage exacerbations. If observed, the treatment plan, including discontinuation of the HIF-PH inhibitor or switching to another agent, should be discussed with a diabetologist, nephrologist, and ophthalmologist.

Introduction

Diabetic retinopathy is one of the three major complications of diabetes, alongside diabetic neuropathy and nephropathy, estimated to affect approximately 93 million people worldwide [1]. Diabetic retinopathy causes ischemia in the retina, leading to the release of vascular endothelial growth factor (VEGF), which plays a crucial role in its progression. The occlusion of retinal vessels triggers ischemia in retinal cells, prompting the production of VEGF and subsequent neovascularization [2]. This neovascularization can result in immature neovascular vessels causing retinal and vitreous hemorrhages, fibrosis of the neovascular scaffold leading to tractional retinal detachment, and neovascularization of the iris and corner angle results in neovascular glaucoma.

On the other hand, diabetes causes diabetic nephropathy, a chronic kidney failure [3]. It is estimated that approximately 700 million people globally suffer from chronic renal failure, and one in seven people will develop renal anemia [4, 5]. Renal anemia is caused by decreased erythropoietin production in the kidneys, owing to renal failure. Traditionally, renal anemia has been primarily treated with injectable erythropoiesis-stimulating agents (ESAs); however, a novel class of drugs with different mechanisms of action has recently been developed. Hypoxia-inducible factor-prolyl hydroxylase (HIF-PH) inhibitors represent this new approach to treating renal anemia. By inhibiting the inactivation of HIF1a, these inhibitors increase the production of erythropoietin. Notably, unlike ESAs, which are injectable drugs, HIF-PH inhibitors can be administered orally [6]. HIF-PH inhibitors have the potential to increase VEGF production, which may exacerbate retinal hemorrhage in diabetic retinopathy and age-related macular diseases [7]. To the best of our knowledge, only a limited number of cases reporting the administration of HIF-PH inhibitor use and the subsequent worsening of fundus hemorrhage in diabetic retinopathy have been documented. In this report, we present a case involving the administration of HIF-PH inhibitor, resulting in the exacerbation of retinal hemorrhage in a patient with diabetic retinopathy.

Case Report

A 32-year-old man was referred to an ophthalmologist for the evaluation of ocular complications related to diabetes mellitus. Thirteen years prior to the first visit to our department, he was diagnosed with type 2 diabetes mellitus at the age of 18 years. Initially, we prescribed an oral hypoglycemic drug, but due to poor glycemic control, subcutaneous insulin was introduced 11 years prior to his referral. Over the subsequent years, he visited the hospital once or twice annually, exhibiting poor adherence to treatment, maintaining inadequate glycemic control, and hemoglobin A1c (HbA1c) of 14–16%. One month prior to presentation, he was referred to the Department of Diabetology at our hospital for comprehensive examination and intensified treatment, prompted by the presence of anemia and declining renal function. Glycemic control was very poor, evident by a blood glucose level of 374 mg/dL and glycoalbumin of 34.5%. He was subsequently referred to

our department for a thorough evaluation of ocular complications. Notably, there were no noteworthy details in his ophthalmologic or other systemic histories, aside from his diabetes, allergies, alcohol consumption, and a smoking habit of 10 cigarettes per day over the past 12 years. There were no hypoglycemic episodes. At the first visit, there was a marked improvement in glycemic control, with HbA1c 7.3%, a blood glucose level of 90 mg/dL, and a glycoalbumin level of 30.3%. He was taking diuretics, had hypertension with a blood pressure of 181/94, and had no dyslipidemia. The corrected visual acuity in both eyes was 20/20, and the intraocular pressure in both eyes measured 15 mm Hg. No evident abnormalities were observed in the anterior segment or the intermediate translucent bodies. However, fundus examination revealed multiple scattered retinal hemorrhages and hard and soft exudates in both eyes; then he was diagnosed with PPDR (shown in Fig. 1a, b). Additionally, optical coherence tomography (OCT) imaging showed macular edema and subretinal fluid in both eyes (shown in Fig. 1c, d). An internal examination revealed that the anemia was renal in origin, and the decreased renal function was end-stage renal failure due to diabetes. His macular edema was thought to be affected by not only diabetic maculopathy but also poor renal function. Considering the possibility of improvement of macular edema with medical treatment, the patient was temporarily followed up on macular edema. In response, the ESA darbepoetin alfa (darbepoetin alfa®, 30 mg once a week, Kyowa Kirin, Tokyo, Japan) was started to address renal anemia, following the guidance of the diabetes physician. This intervention commenced 14 days after the first visit. Subsequent fundus examination revealed a reduction in retinal hemorrhage in both eyes (shown in Fig. 1e, f). The patient was then transferred to another hospital for internal medicine and ophthalmology. On day 74, the patient underwent a transition from darbepoetin alfa to an HIF-PH inhibitor, roxadustat (Evrenzo®, 100 mg three times a week, Astellas Seiyaku, Tokyo, Japan), and simultaneously commenced artificial dialysis. By day 88 (14 days after the start of roxadustat), there was no notable change in the retina of the left eye, whereas a fresh retinal hemorrhage was observed in the right eye (shown in Fig. 2a, b). Macular edema improved, and central macular thickness was 232 μm in the right eye and 260 μm in the left eye. At this juncture, the patient's HbA1c measured at 6.4%. No obvious neovascularization was observed, but it was thought to have progressed to PDR. The patient was scheduled to undergo panretinal photocoagulation, but his medical visits were interrupted due to his lack of understanding of his condition. On day 132 (58 days after the start of roxadustat), the retinal hemorrhage worsened further, and a new preretinal hemorrhage was observed in both eyes (shown in Fig. 2c, d). Macular edema did not recur, and central macular thickness was 235 μm in the right eye and 261 μm in the left eye. Roxadustat was discontinued, and the patient was switched to darbepoetin alfa (30 mg once a week). By day 181 (49 days after the cessation of roxadustat), there was an improvement in the retinal hemorrhage (Fig. 2e, f). Macular edema did not recur, and central macular thickness was 234 μm in the right eye and 255 μm in the left eye. The HbA1c on day 181 was 6.2%, leading to a reduction in darbepoetin alfa dosage to 15 mg once per week because of increased hemoglobin levels. On day 201, the fundus hemorrhage further improved, OCT revealed no macular edema or subretinal fluid, and the retina was generally thin (shown in Fig. 3a–d). Fluorescein angiography, however, indicated the presence of multiple neovascular vessels, active fluorescein leakage, and extensive avascular areas in both eyes (shown in Fig. 3e, f). Consequently, the patient underwent pan-retinal photocoagulation. Darbepoetin alfa was continuously administered, and his visual acuity was maintained throughout the course of treatment. On day 358, his corrected visual acuity in the right eye was 20/20 and in the left eye was 20/25. Fundus examination revealed hard/soft exudates in both eyes and recurrent retinal hemorrhage in the left eye.

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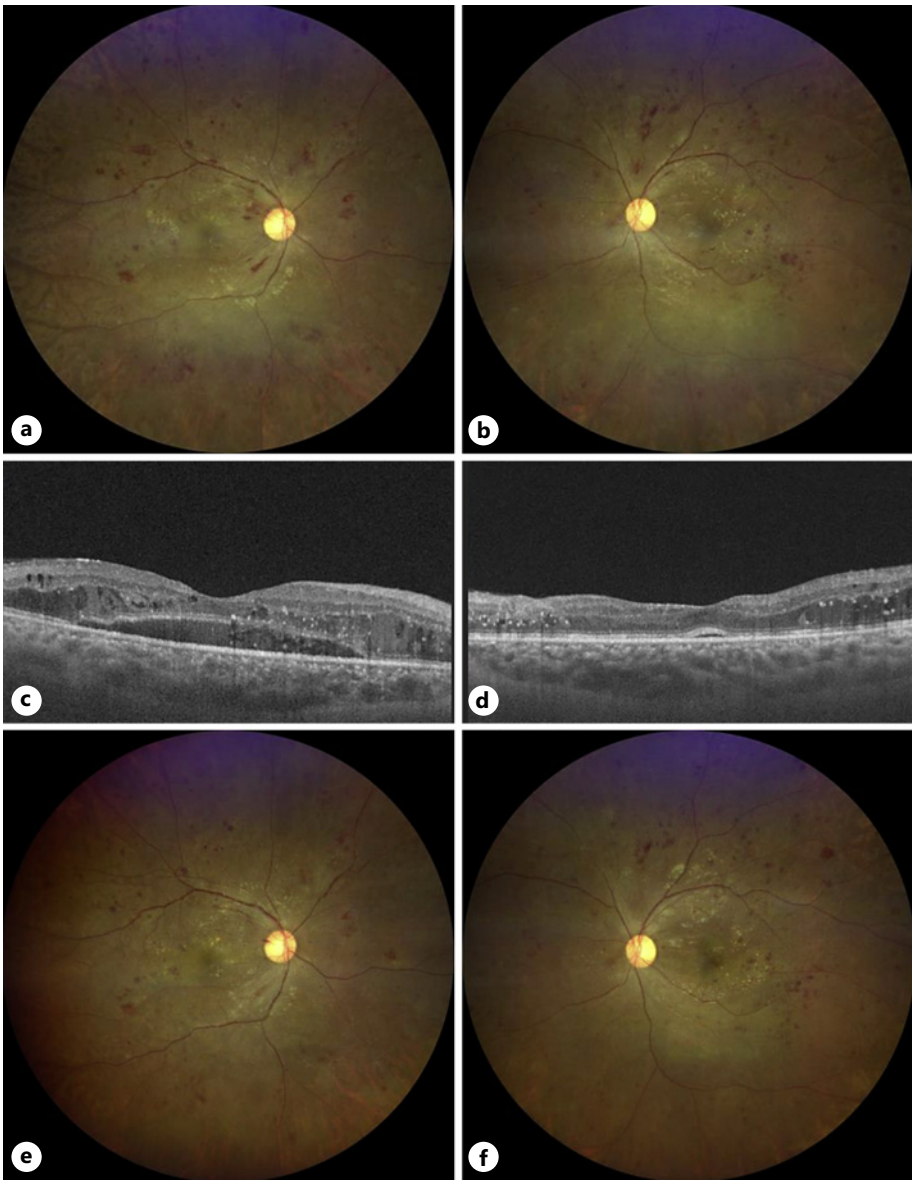

Fig. 1. Findings at first consultation and day 14. **a**, **b** At first consultation, fundus examination revealed multiple scattered retinal hemorrhages and hard and soft exudates in both eyes. **c**, **d** OCT revealed macular edema and subretinal fluid in both eyes. **e**, **f** On day 14, fundus examination showed that the retinal hemorrhage was reduced in both eyes.

Discussion

In this case, the authors experienced an exacerbation of retinal hemorrhage due to diabetic retinopathy simultaneously with the HIF-PH inhibitor administration. HIF-PH inhibitors may increase intraocular VEGF levels.

HIF-PH inhibitors improve renal anemia by increasing erythropoietin production [5]. HIF1a, a transcription factor that regulates the response to hypoxia, remains inactivate and ineffective under normoxic conditions. However, it binds to HIF1b under hypoxic conditions, forming the transcriptionally active HIF1. HIF1, in turn, acts as a transcriptionally active erythropoietin gene, leading to elevated hemoglobin levels by increasing erythropoietin

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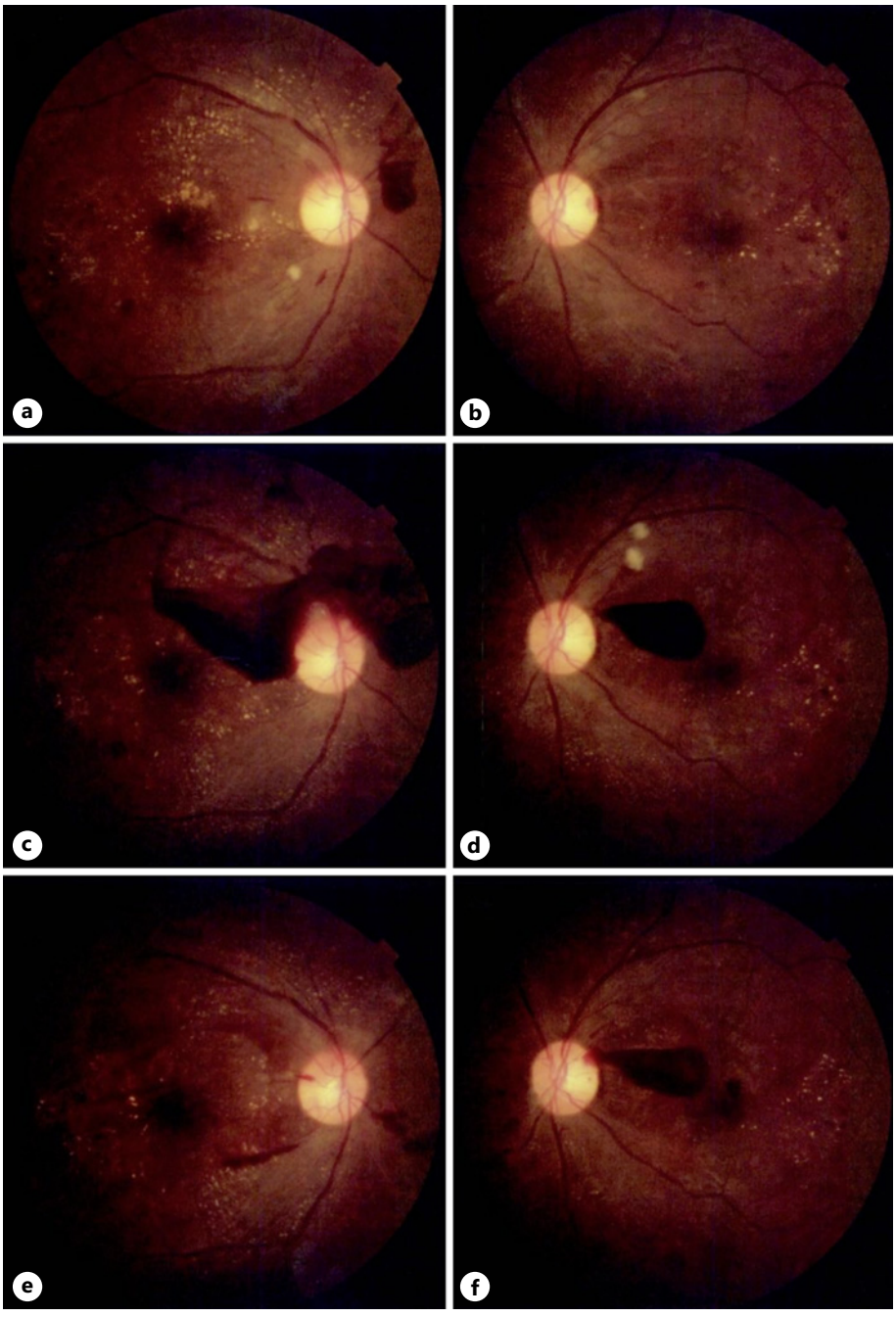

Fig. 2. Findings on days 88, 132, and 181. **a** On day 88, a fresh retinal hemorrhage was observed in the right eye. **b** No remarkable changes were observed in the retina of the left eye. **c**, **d** On day 132, the retinal hemorrhage worsened, and a new preretinal hemorrhage was observed in both eyes. **e**, **f** On day 181, the retinal hemorrhage improved in both eyes after roxadustat was discontinued and switched to darbepoetin alfa.

levels. HIF-PH inhibitors work by inhibiting prolyl hydroxylase and asparaginyl hydroxylase, preventing the inactivation of HIF1a even under normoxic conditions. Therefore, the formation of active HIF1 and the subsequent increase in erythropoietin contribute to the improvement of renal anemia [6]. In contrast, HIF1 activates the transcription of VEGF, which

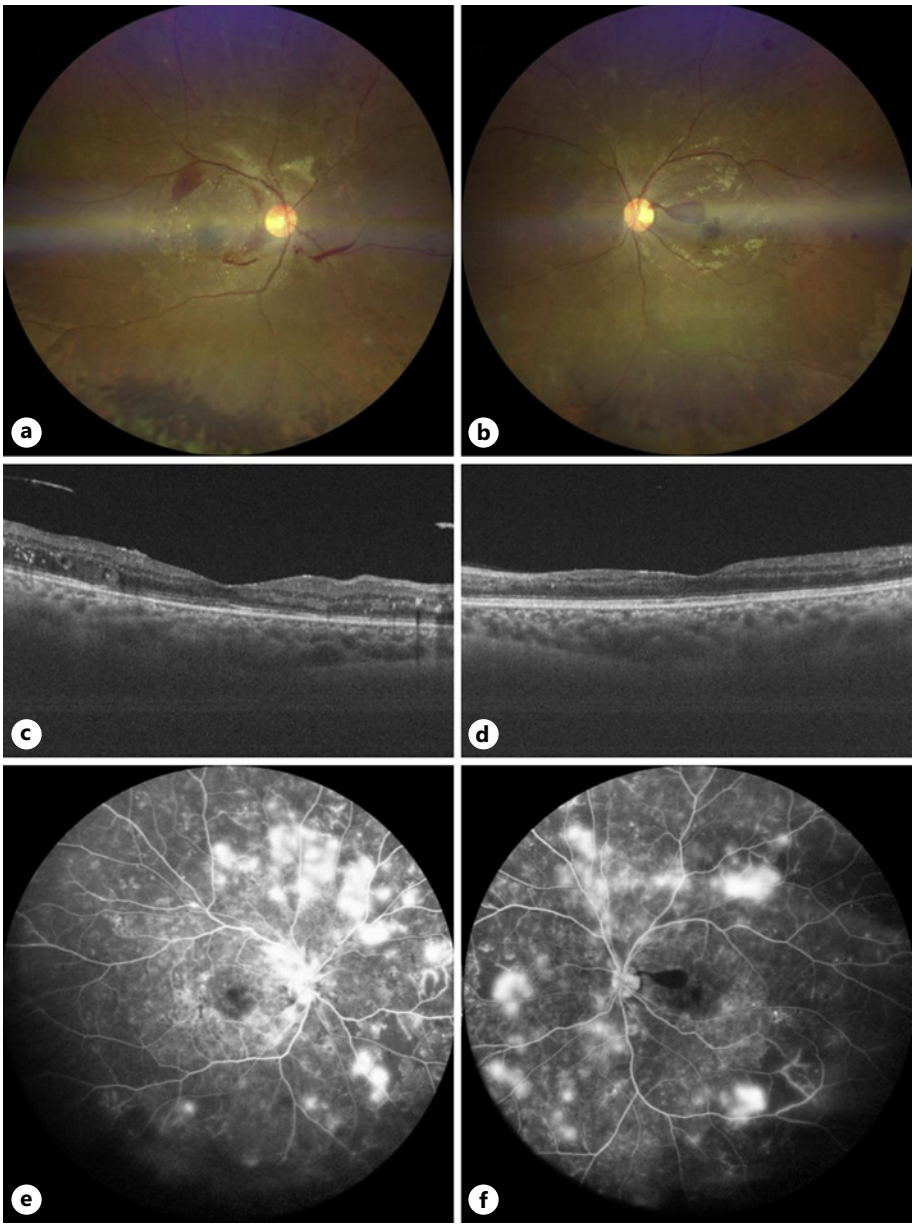

Fig. 3. Findings at day 201. **a**, **b** Fundus hemorrhage had further improved in both eyes. **c**, **d** OCT showed no macular edema or subretinal fluid, and the retina was generally thin. **e**, **f** Fluorescein angiography revealed multiple neovascular vessels, active leakage of fluorescein, and extensive avascular areas in both eyes.

also increases VEGF levels [8]. ESAs, which have been used to treat renal anemia, have also been associated with the risk of retinal hemorrhage; however, they do not directly increase VEGF levels, and there is a concern that HIF-PH inhibitors may pose a risk of further disease progression in diabetic retinopathy and age-related macular degeneration. Therefore, it is recommended to check for retinal hemorrhage exacerbation when administering HIF-PH inhibitors [7].

As for the clinical impact of HIF-PH inhibitors on VEGF, the results of a clinical trial of roxadustat, the drug used in the present case, showed no significant difference in the rate of retinal hemorrhage compared to darbepoetin alfa [9]. By contrast, a phase II clinical

trial of daprodustat, the same HIF-PH inhibitor, reported an increase in blood VEGF levels at higher doses [10]. However, these data are from clinical trials and do not include cases of advanced DR, as in our case. The impact of HIF-PH inhibitors on cases of advanced diabetic retinopathy or those exhibiting elevated levels of intraocular VEGF remains unclear. In the present case, the patient presented with suboptimal glycemic control at the time of referral, advanced diabetes, and complications involving advanced diabetic renal failure. The diabetic retinopathy was suspected to be proliferative diabetic retinopathy, pre-proliferative diabetic retinopathy, or advanced proliferative diabetic retinopathy. Previous reports have shown that the concentration of VEGF in the vitreous of patients with proliferative diabetic retinopathy is higher than that of patients without diabetic retinopathy [11, 12]. It is plausible that the VEGF concentration in the vitreous of this patient was also high. In diabetes, macular edema was also caused by VEGF as a retinopathy. It has been reported that diabetic macular edema worsened after transitioning from an ESA to an HIF-PH inhibitor, with subsequent improvement observed when the drug was discontinued [13]. They suspected involvement of the HIF-PH inhibitor in diabetic macular edema because exacerbation of macular edema was observed after switching from ESAs to an HIF-PH inhibitor was discontinued. In our case, macular edema had improved, but retinal hemorrhage was exacerbated by OCT on day 14 after HIF-PH inhibitor initiation. Dialysis was introduced at the same time as HIF-PH inhibitor initiation, and we consider that the macular edema improved with the effect of dialysis, but the retinal hemorrhage worsened due to the HIF-PH inhibitor. Diabetic retinopathy had already advanced in this patient, and the risk of hemorrhage was high regardless of the presence of the HIF-PH inhibitor. The possibility of early worsening of diabetic retinopathy due to intensified treatment of diabetes mellitus was considered [14]. Dialysis was also initiated at the same time as the HIF-PH inhibitor, potentially influencing the retinal hemorrhage. In addition, no ophthalmological examination was performed at the time the HIF-PH inhibitor was initiated, and no detailed changes in retinal hemorrhage were observed. However, in the current case, the HIF-PH inhibitor was believed to be the cause of the hemorrhage due to a clear increase in retinal hemorrhage in both eyes following its commencement, especially on days 88–132 when glycemic control remained stable. Furthermore, the retinal hemorrhage improved after the HIF-PH inhibitor was discontinued and switched to ESA. Given these findings, we are concerned that the administration of HIF-PH inhibitors may aggravate the condition in patients at a high-risk of hemorrhage, as in the present case. Consequently, based on the course of this case, we recommend considering the discontinuation of HIF-PH inhibitors or exploring alternative drugs, such as ESAs, in similar high-risk patients. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000537913).

Conclusion

In this report, we present a case where the initiation of HIF-PH inhibitors resulted in the exacerbation of retinal hemorrhage in a patient with diabetic retinopathy. This underscores that patients with advanced diabetic retinopathy who are taking HIF-PH inhibitors should be aware of exacerbations of retinal hemorrhage. If exacerbation is observed, it is essential to discuss the treatment plan with diabetologists, nephrologists, and ophthalmologists, considering the discontinuation of the HIF-PH inhibitor or transitioning to an alternative agent. Further studies on the safety of HIF-PH inhibitors are required as evidence accumulates in clinical practice.

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Statement of Ethics

Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

The authors declare no conflict of interests.

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Author Contributions

Nobuaki Ariyoshi designed the study and wrote the initial drafts of the manuscript. Fumiaki Higashijima examined the patient and documented the treatment course. Makiko Wakuta, Tadahiko Ogata, and Manami Ohta contributed to data collection and interpretation and critically reviewed the manuscript. Kazuhiro Kimura is the corresponding author and contributed to the analysis and interpretation of the data and assisted in manuscript preparation. All the authors have read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed in this case report are included in this article. Further inquiries can be directed to the corresponding authors.

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