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Case Report

Anti–Vascular Endothelial Growth Factor Crunch Syndrome in Proliferative Diabetic Retinopathy

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Abstract

A 33-year-old male individual with proliferative diabetic retinopathy (PDR) received a single intravitreal injection of conbercept (Kanghong Inc., Chengdu, China) for vitreous hemorrhage in his right eye. Three days post-injection, his vision deteriorated from 20/25 to hand motion, with anti–vascular endothelial growth factor (VEGF) crunch syndrome progressing to tractional retinal detachment, threatening the macula. Urgent surgical interventions, including vitrectomy, membranectomy, pan-retinal photocoagulation, and silicone oil tamponade, were performed. However, at the 3-month follow-up, visual acuity remained limited to counting fingers. This case highlights crunch syndrome as a rare but serious complication of intravitreal anti-VEGF therapy for PDR, emphasizing the need for careful patient selection and close postoperative monitoring.

Key Words: proliferative diabetic retinopathy, anti–vascular endothelium growth factor, crunch syndrome, conbercept

Abbreviations: IVC, intravitreal conbercept; OCTA, optical coherence tomography angiography; PDR, proliferative diabetic retinopathy; PPV, pars plana vitrectomy; PRP, pan-retinal photocoagulation; TRD, tractional retinal detachment; VEGF, vascular endothelial growth factor; VH, vitreous hemorrhage.

Introduction

Anti–vascular endothelial growth factor (anti-VEGF) crunch syndrome refers to the progression to tractional retinal detachment (TRD) following intravitreal anti-VEGF therapy in eyes with proliferative diabetic retinopathy (PDR) [1]. This syndrome typically manifests as sudden vision loss within 1 to 6 weeks after the injection, with a mean onset of approximately 13 days [2, 3]. Several publications have reported the occurrence of anti-VEGF crunch syndrome following intravitreal bevacizumab and ranibizumab injections. However, to date, there have been no reports linking intravitreal conbercept (IVC) with anti-VEGF crunch syndrome in the treatment of PDR. In this report, we present a case where anti-VEGF crunch syndrome developed in a PDR patient within just 3 days of treatment.

Case Presentation

A 33-year-old male individual with type 2 diabetes had a 10-year history of diabetes mellitus, which was poorly controlled with oral hypoglycemic medication and subcutaneous insulin injections. His glycosylated hemoglobin (HbA1c) was 7.1% (54 mmol/mol), and fasting blood glucose was 7.6 mmol/L (137 mg/dL) (normal reference range: 3.6%-6% [18-42 mmol/mol]; 3.9-6.1 mmol/L [70-110 mg/dL]). He presented with blurry vision in his right eye for 1 week and was diagnosed with PDR. The patient had undergone a pars plana vitrectomy (PPV) and pan-retinal photocoagulation (PRP) on the left eye 6 months prior to consultation due to vitreomacular traction syndrome.

Diagnostic Assessment

The patient's visual acuity on presentation was 20/25 in the right eye and hand motion in the left eye, with normal intraocular pressure. Slit lamp examination revealed a normal anterior segment in both eyes. Fundus photography showed mild vitreous hemorrhage (VH), diffuse epiretinal and subretinal hemorrhages (Fig. 1A and 1B). Optical coherence tomography angiography (OCTA) revealed neovascularization and ischemia in the retinal vessels (Fig. 1C and 1D). Subsequently, the right eye received an IVC injection (10 mg/mL, 0.05 mL) prior to a planned PPV 1 week later. However, he returned with a complaint of sudden vision loss in his right eye 3 days after IVC therapy. His visual acuity dropped from 20/25 to hand motion. Fundus photography revealed worsening VH and progression to retinal detachment, demonstrating crunch syndrome (Fig. 2).

Treatment

The right eye underwent urgent PPV combined with membranectomy, PRP, and silicone oil tamponade. At the time of vitrectomy, the surgeon observed that TRD in the right eye had progressed to involve the macula, with significant VH, widespread fibrovascular proliferation, and scar tissue formation. Given the presence of crunch syndrome, additional intraoperative management included meticulous dissection of fibrovascular membranes to relieve traction, cautious hemostasis to minimize further hemorrhage, and extensive endolaser photocoagulation to reduce the risk of postoperative neovascular activity. Postoperatively, systemic control of

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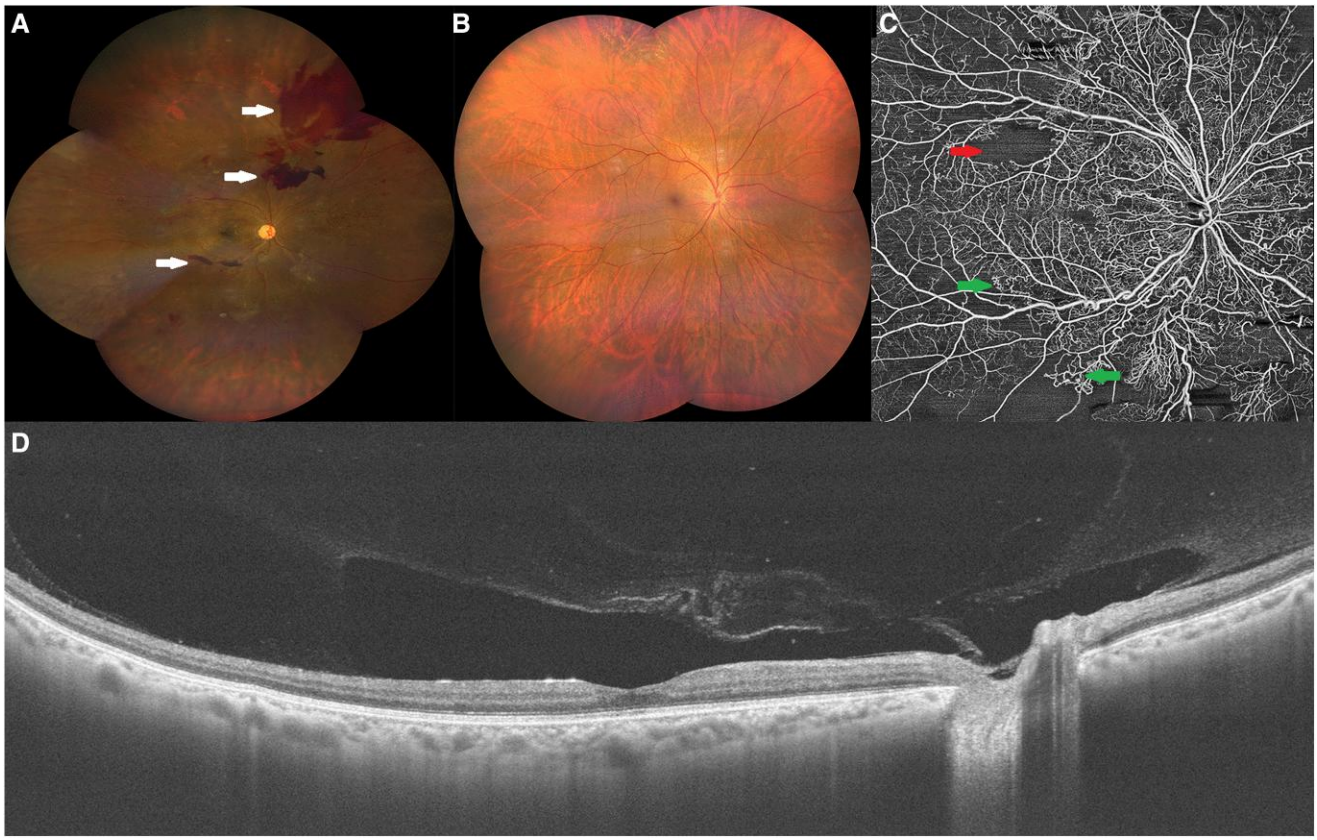

Figure 1. Pre-injection fundus photograph and OCTA images. OCTA: Optical coherence tomography angiography. A, Fundus photograph showing mild vitreous hemorrhage and diffuse epiretinal and subretinal hemorrhages (white arrowheads). B, Fundus photograph showing the normal fundus serving as a control. The fundus image is sourced from the author (Y.Z.), and is published with his permission. C, OCTA revealed neovascularization (green arrowheads) and areas of non-perfusion (the red arrowhead) in the retinal vessels. D, OCTA demonstrated retinal flattening.

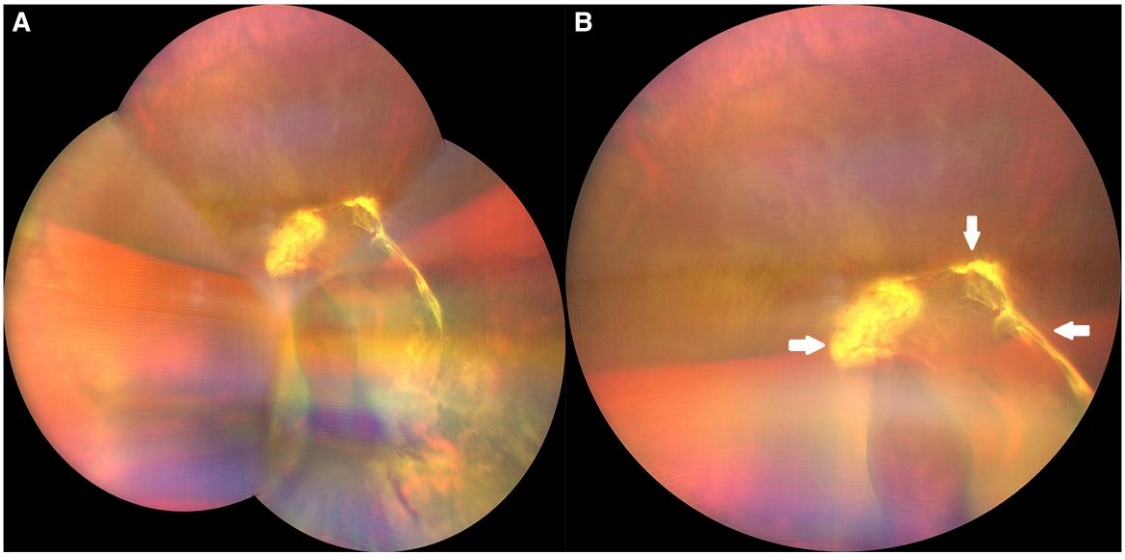

Figure 2. Post-injection fundus photograph images. A, Fundus photograph showing tractional retinal detachment with severe vitreous hemorrhage and fibrosis. B, Semicircular proliferative membranes were noted (white arrowheads).

diabetes and intraocular pressure was reinforced, along with close monitoring for complications, such as recurrent VH, retinal re-detachment, or proliferative vitreoretinopathy.

Outcome and Follow-Up

On the first day after surgery, the right eye experienced a dramatic decrease in visual acuity from 20/25 to counting fingers.

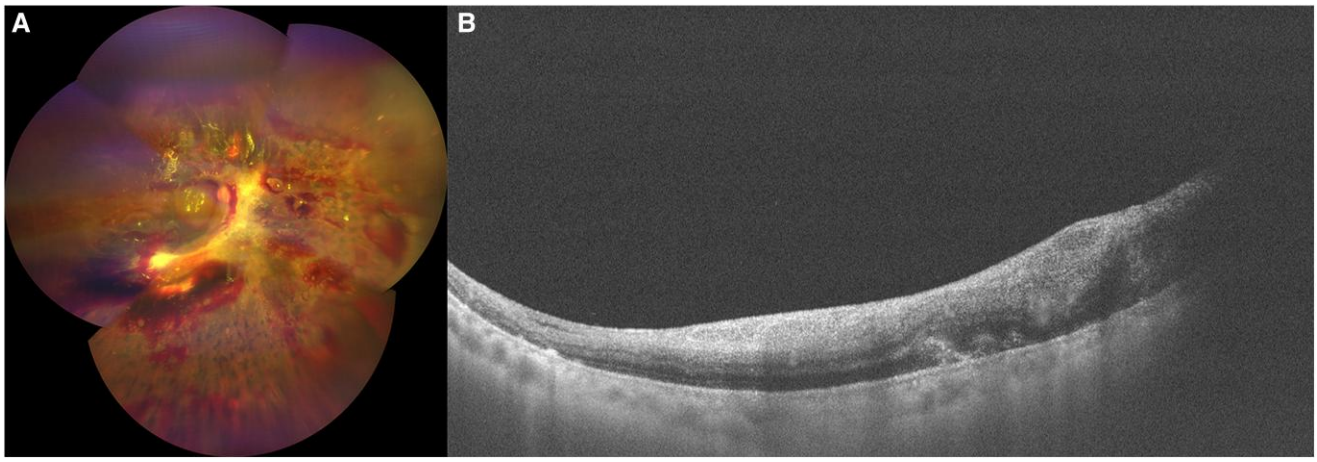

Figure 3. Fundus photograph and optical coherence tomography angiography (OCTA) images taken 3 months postoperatively. A, Fundus photograph showing diffuse retinal hemorrhages and laser spots. B, OCTA showed retinal flattening in the macular area, while interretinal edema persisted.

During the 3-month follow-up, the best-corrected visual acuity (BCVA) in the right eye remained at the level of counting fingers, with retinal flattening confirmed by fundus photography and OCTA (Fig. 3).

Discussion

Crunch syndrome is a rare yet sight-threatening adverse event following intravitreal anti-VEGF agent injection. Our literature research based on the PubMed database revealed that there were only dozens of cases of PDR in which patients developed the crunch phenomenon after intravitreal injection of anti-VEGF agents. These cases were mostly associated with bevacizumab, occasionally with pegaptanib and ranibizumab, and currently there is no reported link with aflibercept. To our knowledge, this is the first case report of crunch syndrome occurring in a PDR patient within 3 days of treatment.

The exact incidence of crunch syndrome and the risk factors for its occurrence in patients with PDR after intravitreal injection of anti-VEGF agents are unclear. However, it has been reported at higher frequencies following PRP [4]. Nevertheless, our patient did not receive PRP treatment before anti-VEGF therapy. Several possible mechanisms could be hypothesized to explain the crunch phenomenon in our patient. First, multiple reports have considered the possibility that crunch syndrome is an independent event secondary to the natural progression of PDR. The pathogenesis of PDR indicates that most PDR eyes will progress over time from angiogenesis dominance to fibrosis dominance. Anti-VEGF drugs are likely to accelerate this fibrosis progression, resulting in crunch formation [5]. Second, blood glucose levels and the duration of diabetes have been confirmed as significant factors contributing to the progression of diabetic retinopathy [6]. As reported in our case, early onset, prolonged duration, and poor blood sugar management may all contribute to exacerbating diabetic retinopathy and ultimately result in the manifestation of a crunch complication. Another possible explanation is that active neovascularization and broad vitreoretinal adhesion might have been causative factors for crunch syndrome formation [7]. Furthermore, the presence of a ring-shaped fibrovascular membrane was more prone to crunch formation [8]. Reviewing the records of our patient, we observed a uniform distribution of neovascularization and proliferative membranes adjacent to the fovea prior to IVC. Coincidentally, anti-VEGF therapy may accelerate the timing and degree of shrinkage of the vitreous and fibrovascular tissue, triggering extreme VH and TRD. From the fundus photography taken after the injection, we can also observe more continuous and severe proliferative membranes. There have been no comprehensive and detailed studies defined and conducted on the crunch syndrome. A few studies have shown possible incidence, risks, and mechanisms of this contingency event. In addition to the limited studies, there are no agreed-upon criteria for inclusion before injection, such as whether PRP treatment has been performed or whether there are preexisting fibrovascular changes in the fundus. Consequently, it is inherently difficult to determine whether the new TRD was a result of the therapy or the natural progression of PDR.

As in prior reports, patients with crunch events experienced unsatisfactory visual outcomes. Anti-VEGF therapy is gaining popularity for the treatment of PDR patients, and IVC before PPV has been reported as significantly improving surgical outcomes in terms of intra- and postoperative complications and visual outcomes [9, 10]. However, our report serves as a warning sign that should be heeded for young PDR patients with active neovascularization and extensive fibrosis.

Given that the contralateral eye had already undergone PPV and PRP for vitreomacular traction syndrome, the risk of developing crunch syndrome in that eye was likely lower, as PRP reduces neovascular activity and fibrovascular proliferation. However, in patients with better visual function in the contralateral eye who have not undergone prior PRP or vitrectomy, there remains a potential risk for similar complications, especially if active neovascularization and fibrovascular membranes are present. Without intravitreal anti-VEGF therapy in the contralateral eye, the disease may progress naturally, potentially leading to complications such as VH or TRD. Thus, careful assessment of the disease stage and individual risk factors should guide treatment decisions, including the need for prophylactic PRP or anti-VEGF therapy in the fellow eye.

The pathophysiology of anti-VEGF crunch syndrome remains a subject of debate, with multiple proposed mechanisms beyond the acceleration of fibrovascular contraction. Some studies suggest that rapid regression of neovascularization following anti-VEGF therapy may lead to abrupt changes

in tractional forces, precipitating retinal detachment in predisposed eyes. Additionally, alterations in intraocular cytokine profiles, particularly reductions in VEGF and increases in transforming growth factor-beta (TGF-β), have been implicated in promoting fibrotic changes and increasing retinal rigidity. The role of preexisting vitreoretinal adhesion patterns and biomechanical stress from longstanding fibrovascular proliferation may also contribute to a sudden decompensation following anti-VEGF therapy. Moreover, recent reports indicate that the type of anti-VEGF agent used may influence the risk of crunch syndrome, with some evidence suggesting that agents with stronger VEGF inhibition, such as aflibercept and conbercept, could induce more pronounced fibrotic responses. Further research is necessary to determine whether specific patient subgroups, such as those with diffuse neovascularization or longstanding ischemic changes, are at particularly high risk for this complication.

Although crunch syndrome after intravitreal anti-VEGF agent injection is quite rare, with the widespread use of anti-VEGF agents, clinicians should keep in mind that such adverse effects might occur after intravitreal injection of the conbercept agent. Therefore, the decision to administer preoperative anti-VEGF treatment should be comprehensively judged. To optimize treatment strategies and minimize the risk of anti-VEGF crunch syndrome, clinicians should consider a thorough preoperative evaluation of high-risk patients. Factors such as extensive fibrovascular proliferation, broad vitreoretinal adhesions, active neovascularization, and poor glycemic control may indicate an increased susceptibility to this complication. In such cases, performing PRP prior to anti-VEGF therapy or opting for early surgical intervention rather than isolated anti-VEGF injection may be more appropriate. Additionally, close post-injection monitoring is crucial, and patients presenting with worsening vision or signs of rapid fibrovascular contraction should be promptly evaluated for urgent surgical intervention to prevent macular involvement and severe vision loss.

To sum up, the crunch syndrome is a rare vision-threatening complication that can occur following intravitreal anti-VEGF injection for PDR. Ophthalmologists should be cautious in evaluating preoperative anti-VEGF therapy for PDR patients.

Learning Points

- Crunch syndrome is a rare yet sight-threatening adverse event following intravitreal anti-VEGF agent injection.
- For PDR patients with proliferative fibrotic membranes in the fundus, ophthalmologists should exercise caution when evaluating anti-VEGF therapy.
- PDR patients may develop crunch syndrome within 1 week after anti-VEGF treatment. Therefore, early and frequent ophthalmological surveillance is recommended following anti-VEGF therapy.

Contributors

All authors made individual contributions to authorship. Z.L. was involved in manuscript preparation and submission; Y.Z. was involved in the diagnosis and management of this patient and responsible for the patient's surgeries. All authors reviewed and approved the final draft.

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Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient.

Data Availability Statement

Original data generated and analyzed during this study are included in this published article.

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