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Longitudinal evaluation of cotton wool spot following rapid glycemic improvement using wide-field multimodal imaging

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ABSTRACT

Purpose: To report a case of a diabetic patient undergoing rapid glycemic improvement characterized by the development and resolution of cotton wool spot (CWS), with detailed structural and vascular assessment using wide-field multimodal imaging, including wide-field color fundus photography and wide-field optical coherence tomography angiography (OCTA).

Observations: A 47-year-old man with poorly controlled Type 2 diabetes mellitus developed CWS in his right eye 3 months after initiating insulin therapy, which coincided with a significant reduction in HbA1c levels. Wide-field color fundus photography and wide-field OCTA were performed before, during, and after CWS appeared. OCTA images revealed an absence of blood flow in the area of CWS during its presence, followed by reperfusion after its resolution. No pre-existing microvascular damage was observed in the area before the development of CWS.

Conclusions and Importance: This case illustrates the potential the utility of multimodal imaging, combining wide-field color fundus photography and wide-field OCTA, as a powerful toolset for the follow-up and management of retinal changes in patients undergoing rapid glycemic improvement. These techniques provide comprehensive insights into retinal vascular and structural changes in diabetic retinopathy, with significant implications for both clinical practice and research.

1. Introduction

Diabetic retinopathy (DR) is a microvascular complication of diabetes that can lead to various retinal changes, including retinal hemorrhage, microaneurysm, cotton wool spot (CWS), intraretinal microvascular abnormality (IRMA), and neovascularization (NV), which can affect both the central and peripheral retina.[1] In some patients undergoing intensive glycemic control, there is a risk of early worsening of diabetic retinopathy (EWDR), characterized by a sudden and acute exacerbation of these retinal lesions.[2]

Wide-field imaging techniques, including wide-field color fundus photography and wide-field optical coherence tomography angiography (OCTA), have proven invaluable in diagnosing and monitoring DR.[3,4] OCTA offers non-invasive, repeatable imaging, enabling detailed follow-up and assessment of retinal blood flow dynamics over time. These imaging modalities provide a comprehensive view of the retina, making it possible to capture the dynamic changes that occur over short periods, such as those seen during EWDR.

We present a case of a poorly controlled diabetic patient who developed CWS 3 months after starting insulin therapy, with subsequent resolution observed over the following month. Using wide-field color fundus photography, we tracked the morphological changes in CWS throughout this period. Additionally, wide-field OCTA allowed us to monitor the retinal vasculature before, during, and after the presence of CWS, noting an absence of blood flow at the lesion sites during CWS and reperfusion following their resolution. This case underscores the potential of wide-field multimodal imaging in capturing the vascular and structural dynamics potentially associated with rapid glycemic improvement.

2. Case report

A 47-year-old man was diagnosed with Type 2 diabetes mellitus (DM) 3 years ago and initially managed with dietary therapy by his

Abbreviations: DR, Diabetic Retinopathy; CWS, Cotton Wool Spot; IRMA, Intraretinal Microvascular Abnormality; NV, Neovascularization; EWDR, Early Worsening of Diabetic Retinopathy; OCTA, Optical Coherence Tomography Angiography; DM, Diabetes Mellitus; HbA1c, Hemoglobin A1c; FA, Fluorescein Angiography; NPA, Non-Perfusion Area; VEGF, Vascular Endothelial Growth Factor.

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primary care physician. Despite an HbA1c of 7.2 % a year ago, irregular follow-ups led to worsening glycemic control, with a random blood glucose of 573 mg/dl and his HbA1c rising dramatically to 15.5 %. He was subsequently referred to our diabetes department, diagnosed with diabetic ketosis, and started on insulin therapy. At the start of treatment, the patient underwent his first ophthalmologic examination as part of an initial DR screening, which revealed no signs of DR.

Following initiating insulin therapy, his HbA1c dropped to 8 % after 1 month. Over the subsequent months, his HbA1c levels improved to 6.3 % at 3 months, 6.2 % at 6 months, and stabilized at 6 % at 9 months.

No signs of DR were observed during the first month of treatment. However, CWS was identified in the right eye at the three-month follow-up without any associated hemorrhage (Fig. 1). The left eye remained stable, showing no signs of retinopathy progression. Systemic evaluation at the time showed normal blood pressure (103/68 mmHg), preserved renal function (serum creatinine 0.88 mg/dL, eGFR 71 mL/min/1.73 m^2), and no anemia (hemoglobin 16.4 g/dL). This presentation was suggestive of EWDR potentially associated with rapid glycemic improvement. By the fourth month, the CWS had resolved, and subsequent 6- and 9-month examinations showed no signs of retinopathy in either eye.

Wide-field color fundus photography (Clarus 500, Carl Zeiss Meditec AG, Jena, Germany) and 12 × 12 mm wide-field OCTA (PLEX Elite 9000, Carl Zeiss Meditec, Dublin, California, USA) of whole retina were performed before CWS development (at baseline, 1 week, and 1 month), during its presence (at 3 months), and after its resolution (at 4, 6, and 9 months). The location where the CWS later formed was included within the imaging area, allowing for the evaluation of retinal blood flow before its emergence. Notably, no blood flow reduction was observed at the site before the CWS's formation. During the presence of the CWS, blood flow was absent at the affected site, with subsequent reperfusion observed after its resolution (Fig. 2).

3. Discussion

In this case, using wide-field multimodal imaging, including wide-field color fundus photography and wide-field OCTA, allowed for detailed observation of the structural and vascular dynamics associated with the development and resolution of CWS in a patient with type 2 diabetes mellitus undergoing rapid glycemic control. Monitoring the formation and resolution of CWS provided critical insights into the underlying pathophysiology of EWDR, particularly the vascular changes occurring during this period.

CWS is commonly considered a localized swelling in the retinal nerve fiber layer (RNFL) due to retinal ischemia.[5] In DR, CWS has traditionally been regarded as a marker of moderate or severe retinopathy.[6] However, it has also been reported as an isolated finding, particularly in the case of severe glycemic imbalance.[7] This patient had marked hyperglycemia at baseline without any signs of DR on initial ophthalmologic examination. After three months of insulin therapy, CWS developed in the right eye as a solitary lesion without associated hemorrhages or other DR features. At the time of CWS development, blood glucose levels had normalized, and systemic evaluations excluded other potential causes, such as hypertension, renal dysfunction, or anemia. These findings suggest that this episode of CWS may represent an isolated manifestation of EWDR associated with rapid glycemic improvement. Although EWDR is often characterized by worsening of DR features, including CWS, IRMAs, and macular edema,[8] this case highlights the potential of wide-field multimodal imaging to detect localized changes such as isolated CWS, which might otherwise go unnoticed.

Historically, fluorescein angiography (FA) and traditional OCTA have depicted CWS as localized non-perfusion areas (NPA); however, the precise temporal changes in retinal blood flow leading to their formation have not been thoroughly documented.[9–11] This gap in documentation primarily arises because FA, which requires the use of contrast agents, is invasive and unsuitable for frequent monitoring. Traditional OCTA, although non-invasive, has a limited field of view. Recently, this limitation has been addressed by the advent of wide-field OCTA, which allows for frequent, non-invasive evaluation of retinal circulation dynamics across a broad area of the retina.[4,12] In our case, wide-field OCTA facilitated detailed, serial observations of retinal blood flow at the CWS site, both before and after its formation. Notably, no significant hypoperfusion was observed in or around the affected area before CWS development, and subsequent imaging revealed reperfusion following its resolution. Previous studies using FA have identified two mechanisms for the reperfusion of avascular areas: the recanalization of previously occluded vessels and the development of intraretinal neovascularization.[13] In this case, the fine vascular structures observed after the CWS resolved closely resembled the capillary structures present before the CWS's formation, without the irregularities typical of neovascularization or IRMA.[12] These findings suggest that the observed reperfusion was likely due to vessel recanalization rather than neovascularization.

While DR is fundamentally a microvascular disease, the development of CWS in an area without pre-existing microvascular damage, as observed in this case, suggests that EWDR may involve mechanisms

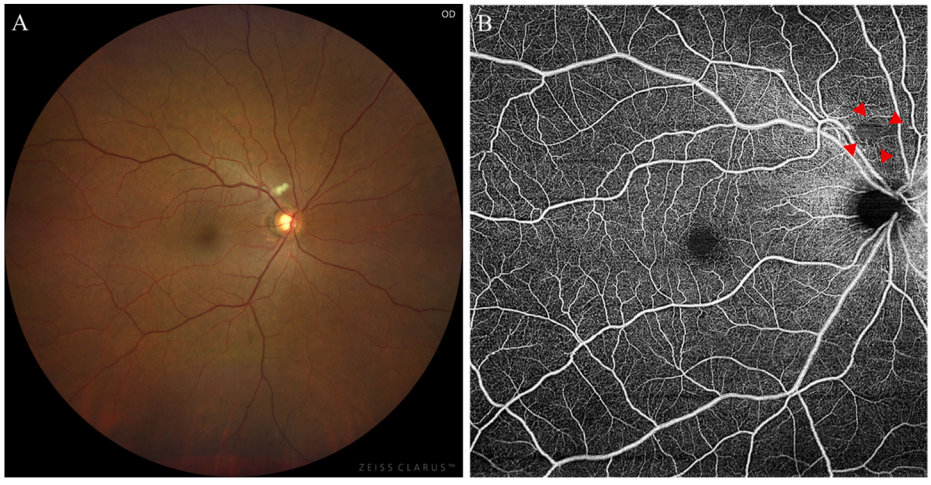

Fig. 1. Color fundus photograph and 12 × 12 mm optical coherence tomography angiography (OCTA) image of the right eye depicting a cotton wool spot (CWS). A: Wide-field color fundus photograph shows a CWS in the superior temporal region, adjacent to the optic disc. The surrounding retinal vasculature appears intact, with no evidence of associated hemorrhage. B: 12 × 12 mm en-face OCTA image of the whole retina highlights the absence of blood flow in the area corresponding to the CWS observed in panel A. Red arrowheads indicate the non-perfusion area, confirming localized ischemia at the site.

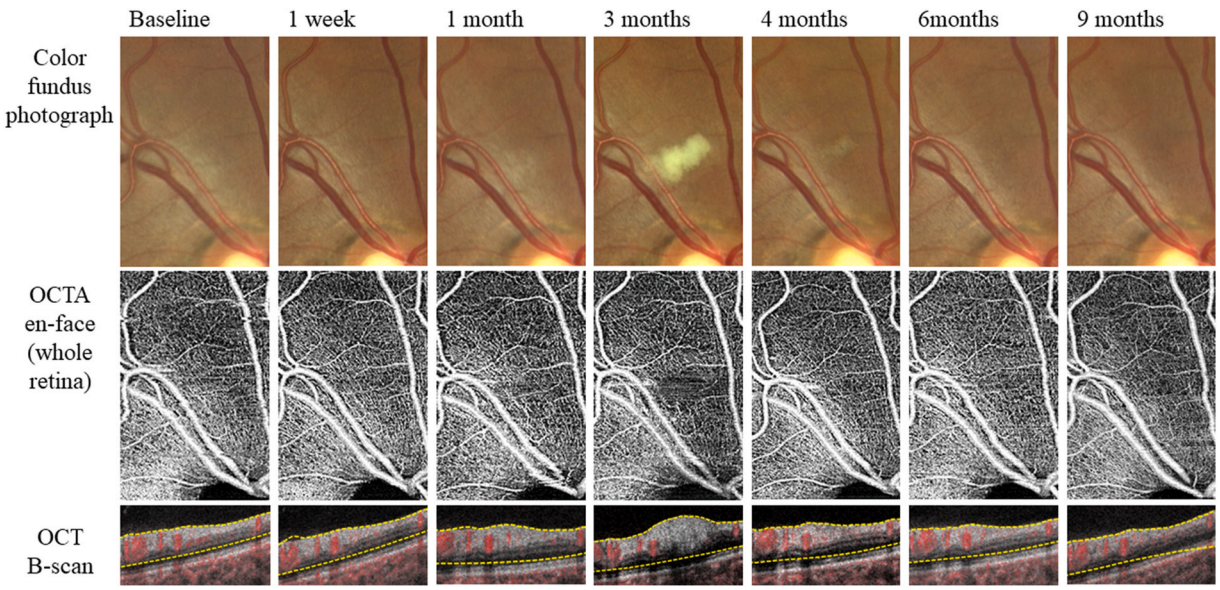

Fig. 2. Serial imaging of the right eye demonstrating the progression and resolution of cotton wool spot (CWS) over time. The top row presents color fundus photographs at baseline, 1 week, 1 month, 3 months, 4 months, 6 months, and 9 months. The CWS is first evident at the 3-month mark, gradually resolving by the 4th month. The middle row depicts corresponding 12 × 12 mm en-face optical coherence tomography angiography (OCTA) images of the whole retina, where the absence of blood flow in the CWS region is apparent during its presence, followed by reperfusion as the CWS resolves. The bottom row displays OCT B-scan images, revealing the thickening of the inner retinal layers during the presence of CWS, which subsequently normalizes as the CWS disappears. The red color indicates "angio flow," representing the presence of blood flow. No blood flow is observed at the 3-month mark in the CWS region.

distinct from the typical pathogenesis of DR.[14,15] The mechanisms underlying EWDR remain unclear, several hypotheses have been proposed.[16–18] One hypothesis suggests that the rapid reduction in blood glucose levels triggers an increase in insulin-like growth factor 1, leading to vascular endothelial growth factor (VEGF) upregulation, which subsequently causes reduced blood flow and increased vascular permeability.[16] Additionally, insulin itself may elevate hypoxia-inducible factor 1-alpha levels, further promoting VEGF production and contributing to these vascular changes.[17] Another hypothesis posits that the absence of glucose's neuroprotective effects during hypoglycemia may influence EWDR development.[18] Many of the fundus changes observed in EWDR are known to be transient, with 51 % of these lesions spontaneously resolving within 18 months.[2] The recanalization of previously occluded blood flow observed in this case aligns well with the known clinical course of EWDR, suggesting that changes in blood flow may play an important role in the pathogenesis of EWDR.

The pathogenesis of CWS has been attributed to various mechanisms, including localized infarction of the retinal nerve fiber layer (RNFL) and axoplasmic stasis with the accumulation of cytoid bodies in the axons of retinal ganglion cells caused by broader retinal ischemia.[19,20] Particularly, the axoplasmic stasis caused by broader retinal ischemia challenges the concept of CWS as merely a localized infarction, suggesting instead that it may represent a sentinel lesion against a background of widespread retinal ischemia. According to this hypothesis, focal NPAs observed on FA and OCTA corresponding to CWS may not indicate actual ischemic changes but rather result from shadowing effects caused by inner retinal thickening. In this case, OCT B-scan revealed inner retinal thickening at the site of CWS during its formation. However, no significant ischemic changes were observed across the broader area captured by wide-field OCTA. This case does not provide definitive evidence to support either hypothesis; however, the absence of ischemic changes around the site of CWS during rapid glycemic improvement, despite its typical association with retinal ischemia, presents an intriguing perspective.

Fortunately, the CWSs resolved without leading to more severe complications in this case. However, in cases where CWS spreads extensively, resulting in irreversible NPA, or where NVs and proliferative changes occur, treatment options such as pan-retinal photocoagulation may need to be considered.[21] Wide-field multimodal imaging, which combines wide-field color fundus photography and wide-field OCTA, remains a valuable tool in evaluating and managing these retinal changes. For patients undergoing rapid glycemic control, early ophthalmologic evaluation and continuous monitoring of retinal circulation are crucial to managing and mitigating potential complications, including EWDR.

Although this case provides valuable insights, it has several limitations. As a single case report, its findings cannot be generalized. To demonstrate the utility of multimodal imaging in monitoring and elucidating the pathophysiology of EWDR, further prospective studies with a larger cohort of diabetic patients undergoing rapid glycemic control are currently underway.

4. Conclusion

This report presents a case of CWS development and resolution in a patient undergoing rapid glycemic improvement, where the retinal vascular and structural changes were meticulously evaluated using wide-field multimodal imaging. The findings in this case suggest that CWS in EWDR can occur without pre-existing microvascular damage. Additionally, using wide-field multimodal imaging, including OCTA and color fundus photography, is crucial for the detailed monitoring and management of such cases, providing essential insights that can enhance clinical practice and research in DR.

CRediT authorship contribution statement

Ken Hoshiyama: Writing – original draft, Visualization, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Takao Hirano:** Writing – review & editing, Conceptualization. **Yoshiaki Takahashi:** Investigation. **Yoshiaki Chiku:** Investigation. **Toshinori Murata:** Supervision.

Patient consent

The patient provided written consent to publish this case report. No personal identifying information is included.

Authorship

All authors attest to meeting the current International Committee of Medical Journal Editors (ICMJE) criteria for authorship.

Data statement

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to ethical reasons.

Glossary

No specialized terms requiring additional explanation are present in this manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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