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Sudden blurring of vision and micropsia following acute hot pepper consumption: A case report

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ABSTRACT

Background: Retinal hemorrhages are typically considered a major ocular diagnostic sign of underlying systemic vascular disorder. Capsaicin is a bioactive component of chili peppers used in most countries. Capsaicin crosses the blood–brain barrier in an efficient manner. Exposure to dietary capsaicinoids is frequent and often considerable. The presumed lack of capsaicin toxicity in the diet does not rule out the possibility of rare adverse effects on the central nervous system, particularly the retina, as outlined in this report.

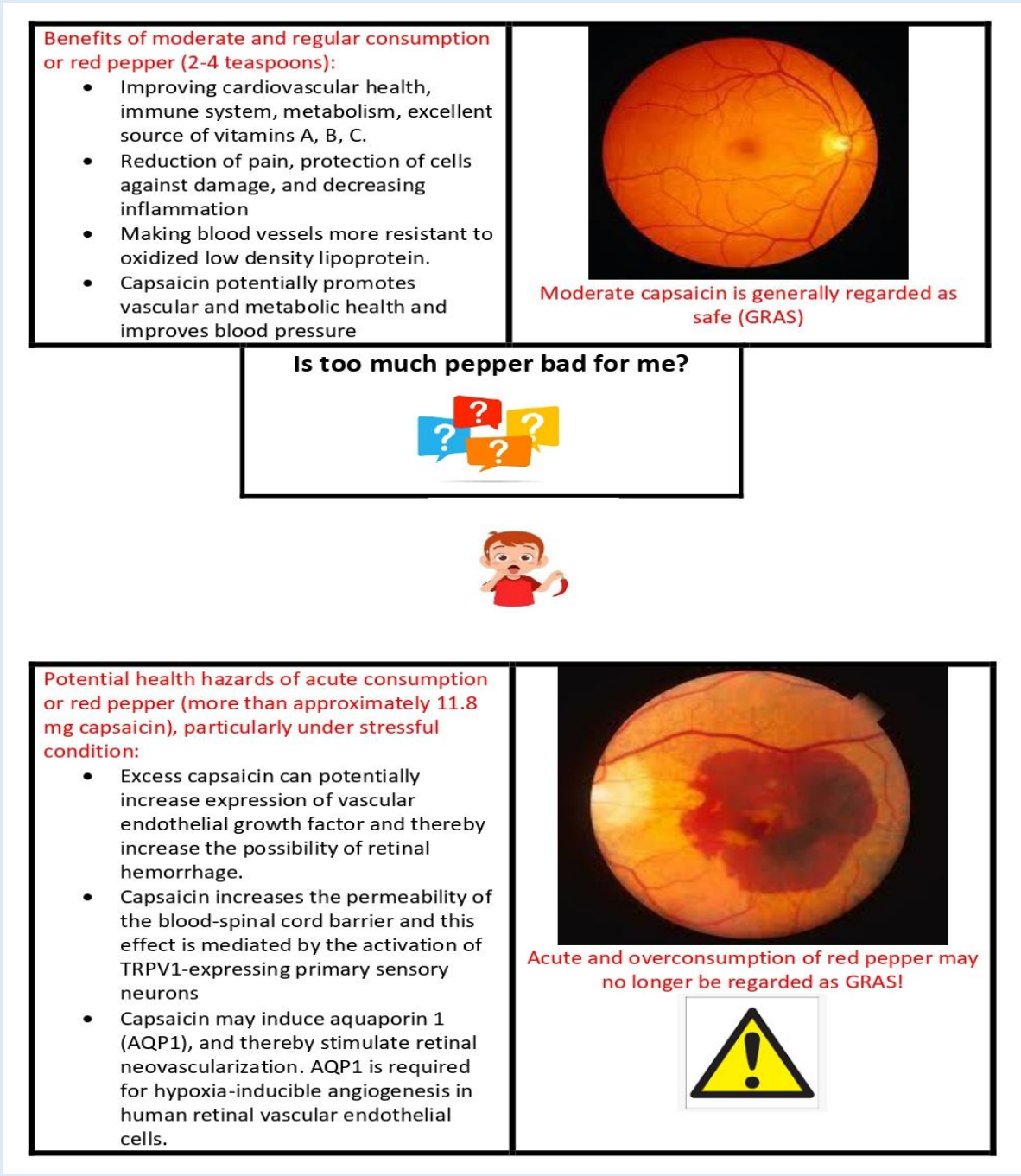
Objective: The purpose of this case report is to describe the ocular issues occurring to a man who developed retinal hemorrhage following overconsumption of hot chili.

Methods: A case of a 34-year-old man, who reported sudden blurring of vision and micropsia in his left eye following ingestion of a considerable amount of red pepper.

Results: The case study suggests that acute or chronic consumption of substantial amounts of hot red pepper in individuals with high reactivity towards TRPV1 agonists and/or higher expression of TRPV1 receptors in retinal ganglion cells causes retinal neovascularization.

Conclusion: Acute consumption of large amounts of red pepper in susceptible individuals may harm vision.

Keywords: Capsaicin; Red Chili; Retinal hemorrhage; Optometry; Micropsia



Graphical Abstract: Sudden blurring of vision and micropsia following acute hot pepper consumption

INTRODUCTION

Retinal hemorrhages are typically considered a major ocular diagnostic sign of underlying systemic vascular disorder. They range from small dot and blot to large sub-hyaloid hemorrhages. The size, distribution and location of hemorrhages indicate etiology and underlying systemic conditions such as hematologic disorders, vascular disease, and infections, dyscrasias, hypoxia or trauma. In rare cases, hemorrhages are also expressed in idiopathic form. Most require detailed systemic work-up to discover underlying causes. Management entails precise observation, treating the

initial cause, and intraocular management to diminish neovascularization and ischemic sequelae following hemorrhages [1].

Capsaicin is a bioactive component of chili peppers. Capsaicin is a capsaicinoid. Capsaicinoids are bioactive compounds and are responsible for the hot taste of chili peppers. Dietary intake of capsaicin can reach as much as 0.5–4 mg/kg/day. Natural sources of capsaicinoid family are classified as GRAS (Generally Regarded as Safe) substances [2], even though there is often no scientific basis for that belief. Capsaicin can function as a double-edged sword. From the perspective of retinal vascular disease, it may improve diabetic retinopathy by activating vanilloid receptor type 1 (TRPV1) and suppressing the PPARγ-poldip2-Nox4 pathway in rat model [3]. Also, capsaicin, through the release of endogenous somatostatin, has anti-inflammatory and retinal protective effects on ischemia-induced injuries [4]. On the other hand, findings from in culture studies have shown that cannabinoids can induce apotosis and elevate P2X7 receptor signaling in chick embryo retinal progenitor cells [5].

As shown in experimental animal studies, capsaicin crosses the blood–brain barrier in an efficient manner [6,7]. Most pepper constituents metabolize in the liver, with the lung being the second organ metabolizing the capsaicin. Capsaicin is also metabolized in the skin and intestine [7]. It is commonly believed that capsaicin is completely metabolized within 20 minutes in rat and human microsomes [8]. Dietary intake of capsaicinoids is considerable [2]. Here, we present a case of a 34-year-old man who reported sudden blurring of vision and micropsia on his left eye following ingestion of a large amount of red pepper. The presumed lack of toxicity of capsaicin in the usual diet does not preclude rare adverse effects related to its actions on the central neural system particularly on the retina, thus we will present a specific case in this short paper.

CASE REPORT

After a stressful period, a 34-year-old, slightly myopic male university teacher reported sudden blurring of vision and micropsia on his left eye. He also reported consumption of 10 grams of red pepper powder (Jalapeño type) and two fresh hot red peppers (Jalapeño type) shortly before occurrence of subjective symptoms. This is roughly equivalent to 11.8 mg capsaicin according to Weisenfelder et al [9]. At the first visit the best corrected visual acuity was RE: 6/12, LE: 6/9. Recorded intraocular pressure (IOP; Goldman applanation tonometer) RE: 40 mm Hg, LE: 39 mm Hg. There was no history of trauma, steroid use, or any other cause for secondary micropsia. There was no family history of secondary micropsia or myopia. The patient mentioned he had refractive surgery to correct myopia.

Ophtalmoscopic examination and OCT revealed normal appearance of the right fundus and sharp bordered, half disc-sized, sub-pigment epithelial edema involving the fovea on the left eye. Fluorescein angiography revealed one leakage. Diagnoses revealed hemorrhage in the left retina and recurrent episodes of subretinal fluid accumulation (Figure 1A).

Intravitreal Avastin (bevacizumab) injection (1.25 mg in 0.05 ml) was performed three times. Avastin is a monoclonal antibody that targets vascular endothelial growth factor A (VEGF-A) and processes anti-angiogenic activity. After Avastin treatment, his vision acuity and fundus condition got better within about 10 days and about six months later the diagnosis was “inactive central serous retinopathy” by the local ophthalmologist. However, during the next 3 years, observation identified small relapses following red pepper consumption. Approximately 3 years after the beginning of the disease the patient received further intravitreal Avastin injection. Although advised to stop eating red pepper the patient failed to follow this recommendation. The patient provided written consent for this report. Figures 1A- 1C demonstrate the optical coherence tomography (OCT) of the left eye on 2nd December 2008 (3 days after the occurrence of the problem, i.e., the day patient went to the eye hospital), 10th March 2010, and 27th November 2010.

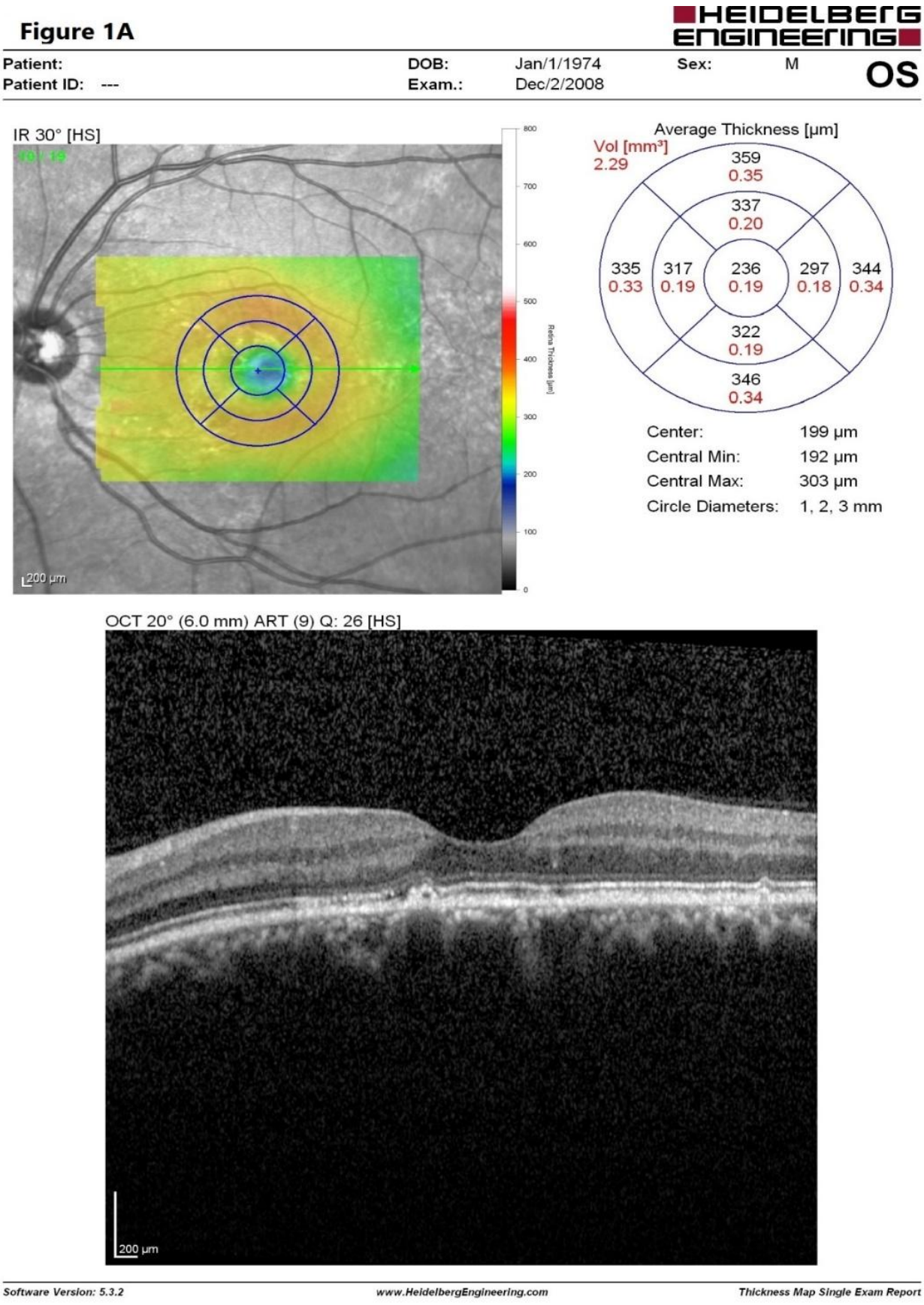


Figure 1A (2nd December 2008): Optical coherence tomography of the left eye on 16th March 2010, when the patient was under severe stress and consumed a high amount of hot pepper (3 days after acute hot pepper consumption).

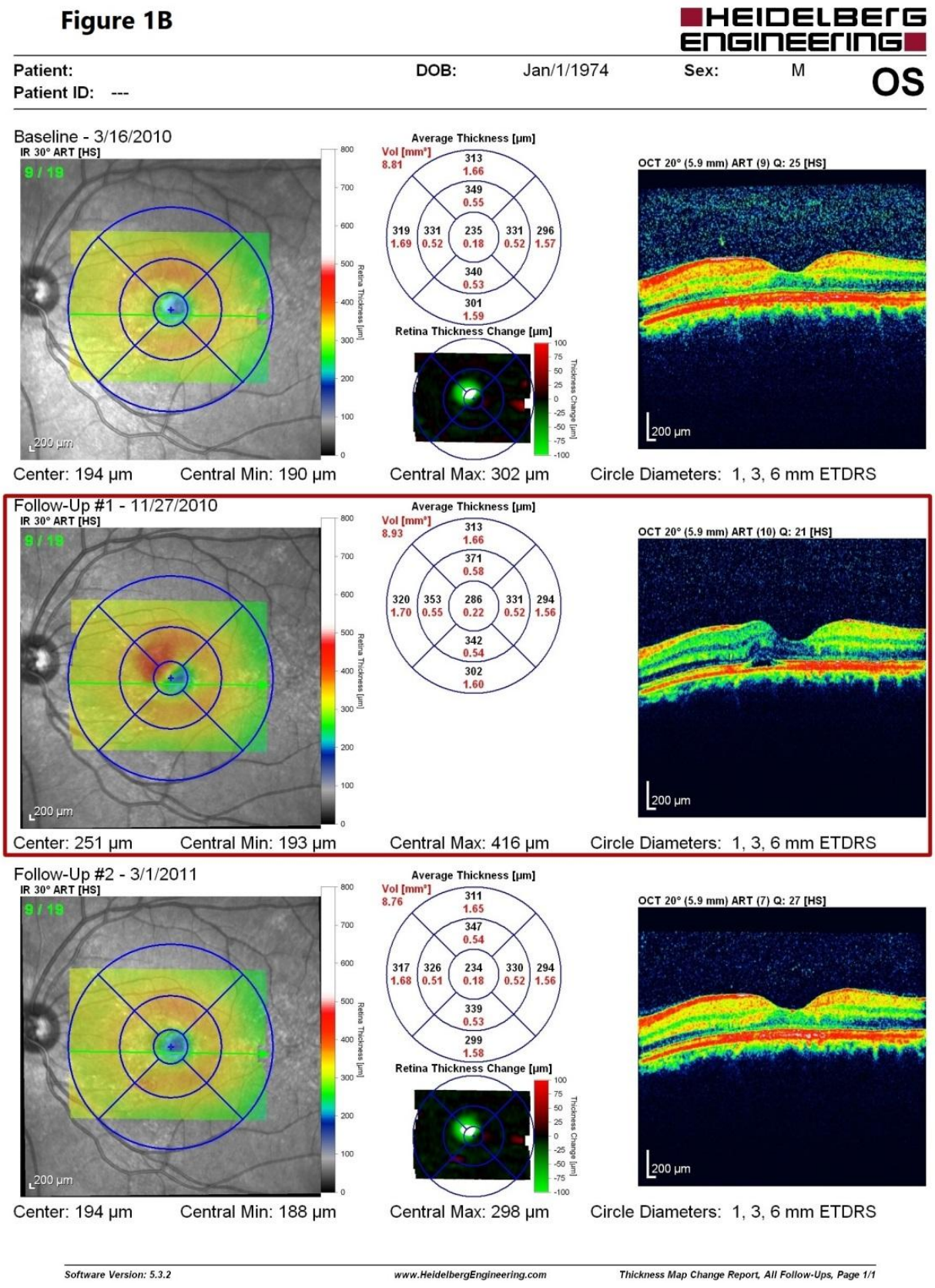


Figure 1B (16 March 2010). Optical coherence tomography of the left eye, approximately 26 months after the first retinal hemorrhage. Retinal hemorrhage occurs again after a similar scenario. Patients failed to follow advice regarding the need to stop overconsumption of red pepper.

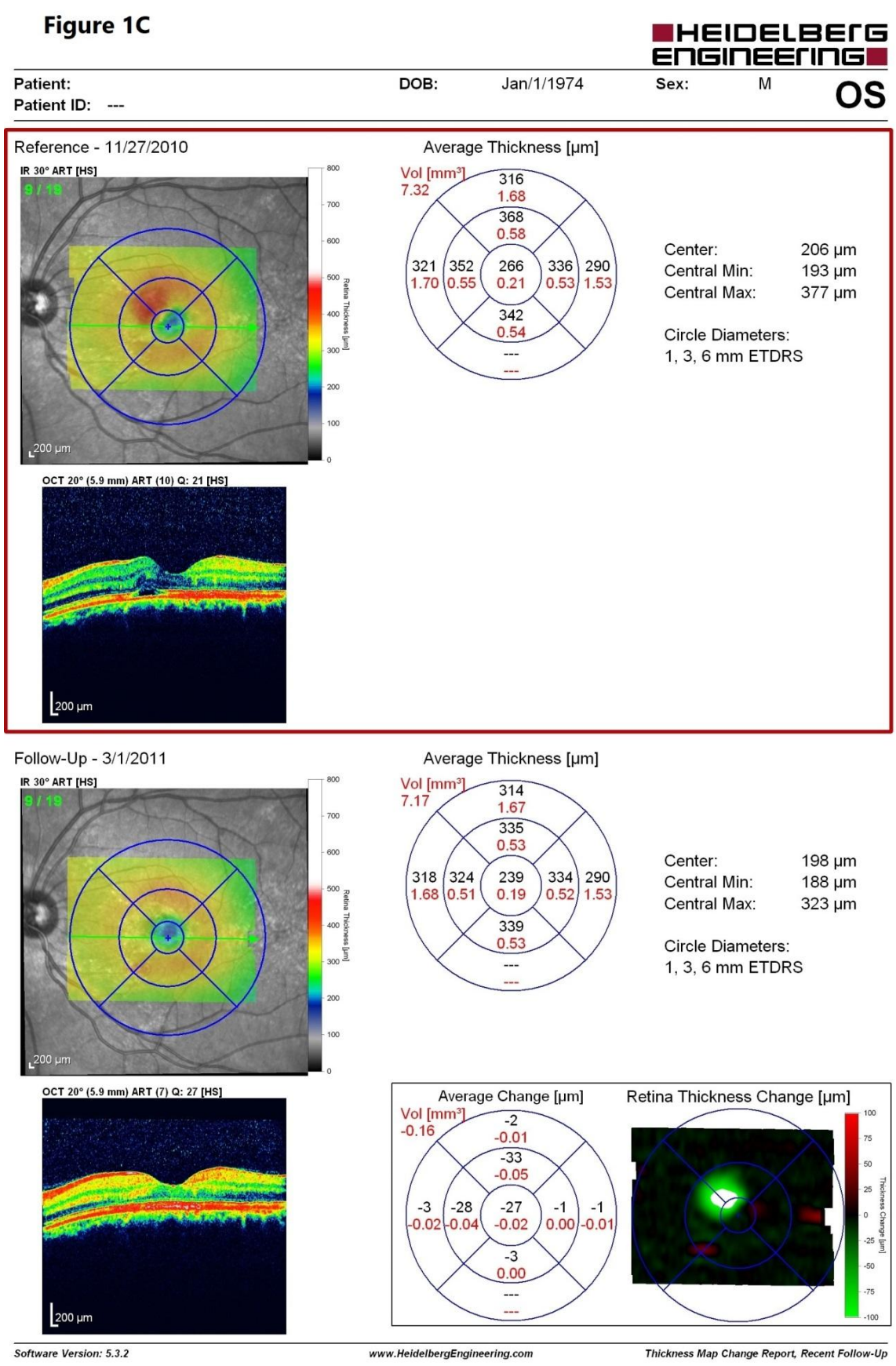
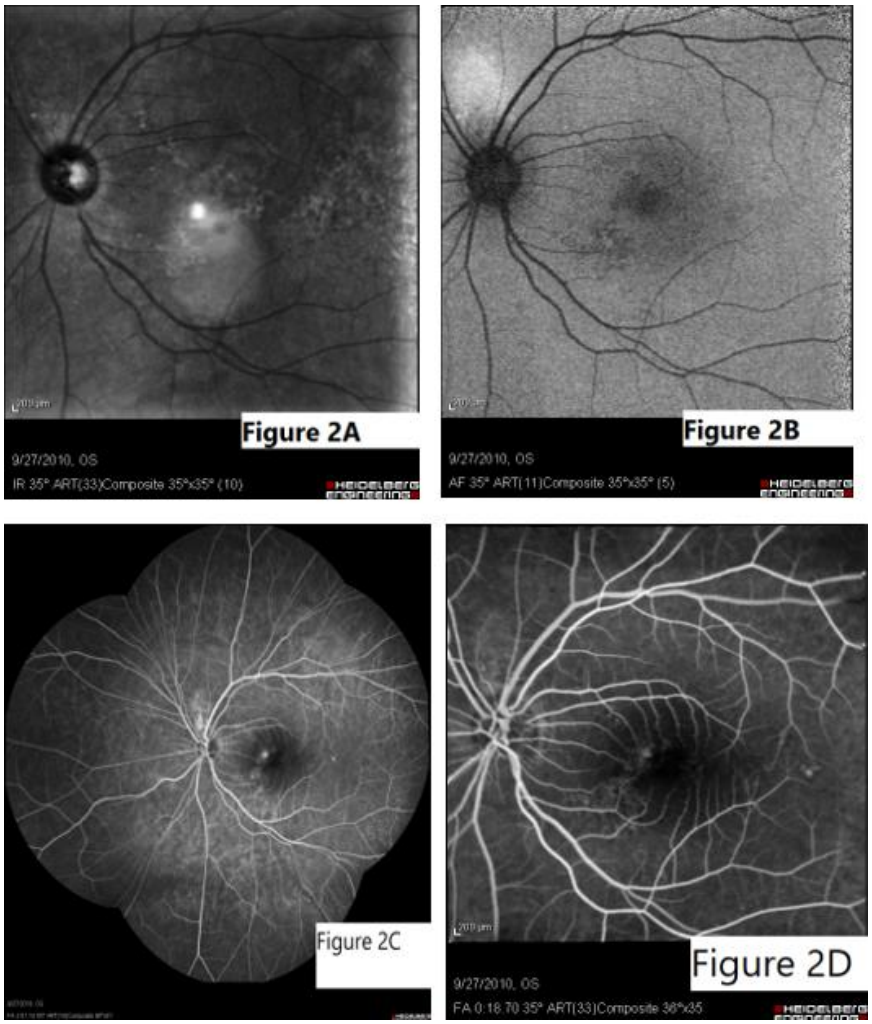


Figure 1C (27th November 2010). Retina looks relatively healthy after avoiding red pepper overconsumption.



Figures 2A-2D demonstrate the angiography of the left eye from different angles, Date: 27th September 2010.

DISCUSSION

For choroidal neovascularization, 34 years old represents a young age of onset. At such age, a common cause of recurrent subretinal fluid induced by stress is central serous chorioretinopathy (CSC), but that is not associated with retinal hemorrhage, which would rather be more suggestive of wet macular degeneration with choroidal neovascularization [10]. Choroidal neovascularization is indeed most common among the elderly, often with macular drusen present in the macula. It can also arise in highly myopic individuals, or those with preexisting macular scars, such as those caused by histoplasmosis or other forms of inflammation, such as multifocal choroiditis. Choroidal neovascularization can also develop from areas of scarring caused by repeated episodes of CSC [10]. In that situation, stress could have caused episodes of CSC, and macular scars from CSC could later evolve into wet macular degeneration [11,14]. Avastin could minimize fluid for both CSC and wet macular degeneration [15,16]. Therefore, it is important to utilize individualized therapy with Avastin in wet age-related macular degeneration. To the best of the authors' knowledge, although people consume pepper in substantial amounts, there have been no reports on the deterioration of CSC or wet macular degeneration after eating peppers. Researchers have not addressed whether red pepper consumption in stressed individual

causes deterioration of CSC or wet macular degeneration because of (i) the lack of any hypothesis connecting these situations to each other, and (ii) the extremely low prevalence of these conditions which might occur concomitantly.

It is questionable whether pepper intake alone induces retinal neovascularization and retinal ganglion cell death in humans. Pathogenesis of retinal neovascularization is multifactorial; high pepper intake may promote the disease progression, but hot pepper intake may only function as a trigger of the disease. Most pepper constituents degrade in the liver and currently there is no direct evidence to show that capsaicin reaches the retina in sufficient amounts in humans. There are at least 3 potential possibilities to explain our observation:

(i) The most straightforward explanation for this observation is that retinal issues following capsaicin consumption are not consistent. However, the fact that our patient experienced the same retinal problems three times following considerable amounts of red pepper, merits investigations.

(ii) The second possibility-albeit with low likelihood- is that capsaicin may have been capable of crossing the blood-brain-barrier (BBB). Indeed, there is evidence to support this possibility [6,7,17,18]. After being transported into the portal vein and then into the whole body in both human and rodents, about 5% of unmodified capsaicin crosses the BBB and goes into the brain tissue [17,18]. This suggests that acute consumption of capsaicin could be another rational explanation. This, in turn, may create a further possibility, i.e. there might be individuals who are extremely sensitive or hyper-reactive to high and acute intake of capsaicin. There is also evidence showing that capsaicin increases the permeability of the blood-spinal cord barrier, and this effect is mediated by the activation of TRPV1-expressing primary sensory neurons [19]. If it is conceivable that capsaicin can cross in sufficient amounts in hyper-reactive individuals, then the common belief that red pepper is safe requires reconsideration. This also may affect the design of future studies investigating related ocular conditions, because there is a robust possibility that high intake of red pepper may create uncertainty or bias, particularly in non-randomized clinical trials. This case report may also have implications for the design of capsaicin-related food supplements and drugs, particularly considering high inter-individual differences in capsaicin bioavailability [20] and metabolism, detoxification, and bioactivation of capsaicin as well as alkyl dehydrogenation and oxygenation of capsaicinoids by P450 enzymes [21]. In this regard, it of interest to mention the hypertensive crisis in a 19-year-old man with a prior abundant ingestion of peppers likely associated to a decrease in protecting calcitonin gene-related peptide [22] as well of myocardial infarction due to cayenne pepper pills in a young man [23].

(iii) Another hypothetical explanation for this case report is the involvement of aquaporins (AQPs). Experimental animals have a set of homeostatic mechanisms that continuously work together to keep body-fluid osmolality close to a narrow range (~300 mOsm/kg) [24]. AQPs have been implicated in retinal neovascularization both in

animal models and humans [25-28]. Namely, AQP1 is essential for hypoxia-inducible angiogenesis in human retinal vascular endothelial cells [25]. Relatedly, activating stimuli such as AQPs, protons and temperature synergistically enhance osmosensitivity of TRPV1.

It is established that TRPV1 and TRPV4 channels are involved in retinal angiogenesis [2,28]. Caitriona O'Leary et al [29]. investigated TRPV1 molecular and functional expression in detail in retinal ECs in vivo for the first time. They examined the localization of TRPV1 channels in the retinal vasculature and cultured retinal microvascular endothelial cells (RMECs) of bovine cells. They found that TRPV1 and TRPV4 channels act by modulating tubulogenesis in a specific manner. They subsequently showed that pharmacologic inhibition of TRPV1 or TRPV4 channels can suppress retinal angiogenesis through modulation of tubulogenesis, proving the causal relationship. Further in vitro studies indicated that blockade of TRPV1 and TRPV4 channels did not lead to a detectable effect on VEGF-related angiogenesis or Ca2þ signals. Patch-clamp and PLA and studies showed that TRPV1 and TRPV4 form channel complexes in RMECs. The inhibition of these two channels decreased retinal neovascularization and stimulated physiological revascularization of the ischemic retina in the oxygen-induced retinopathy mouse model [29]. It may also help to note that TRPV1 is predominantly expressed in the horizontal system of the retina in adult vervet monkeys with high similarity to humans in genome and structure [30-31].

In support of this argument, it was recently shown that TRPV4 channels promote vascular permeability in the retinal vein occlusion murine model [30]. These findings are pertinent to the present case report because there is evidence showing that TRPV1 channels are expressed in human retinal microvascular endothelial cells [3,31]. Although pesticides have been reported in red pepper crops [32], and these chemicals have a known noxious effect on redox system and overall body [33], the isolated case suggests ruling out this argument.

Capsaicin, like other natural plants, fermented food, and marine-derived compounds maintain an interesting profile for potential neuroprotective diseases [34-39] as well as in longevity research [40-41]. Nonetheless, the present case report may represent a learning opportunity for the physician and nutritionist to pay some care and understanding. Medicinally speaking, spices have been used for many purposes since ancient times until present day [42-52]. The most striking point is that even in scientific literature more weight is given to useful effects and potential hazards are ignored. This case report is a warning of the risks related to the overconsumption of other commonly used spices which are regarded as GRAS.

Given the information above, acute or chronic consumption of substantial amounts of hot red pepper could be involved in retinal neovascularization in individuals with high reactivity towards TRPV1 agonists and/or higher expression of TRPV1 receptors in retinal ganglion cells. This case report seems to be the one needing great consideration. This provides evidence for our argument that anti(angiogenic) food components can be potentially a major source of bias in the investigation of angiogenesis inhibitors [53]. The pivotal point here is that biological functions of bioactive compounds are greatly influenced by their concentration. This highlights the importance of quantifying and measuring oral intake of bioactive

compounds in clinical trials in study arms. We therefore call for developing and validating a semi-quantitative food frequency questionnaire (FFQ) to gather data on these bioactive components, specifically designed for oncological and ophthalmological research because there is a clear gap in the literature in this regard.

Authors' contributions: RR wrote the initial draft, critically appraised the case report and wrote the case report. GSC helped in the discussion section, FM critically appraised the paper, CA wrote the discussion, and FH interpreted the data. All authors approved the final manuscript.

Availability of data and materials: The data supporting this case report is available upon request.

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