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Volume rendering of superficial Optic Disc Drusen: a possible new Imaging technique using Optical Coherence Tomography Angiography

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Abstract:	Background Optic disc drusen (ODD) are calcified deposits potentially caused by disturbances in axonal metabolism. The clinical course and visual impairment of ODD is usually mild, however, significant ocular morbidity may occur such as visual field defects and retinal haemorrhages. Optic disc drusen may pose a diagnostic dilemma and differentiating these from other entities that can lead to similar compressive axonal distress is imperative. We present a novel technique for three-dimensional (3D) characterisation of superficial ODD based on 3D volume rendering of optical coherence tomography angiography (3DOCTA) scans. Material and methods Optical coherence tomography (Zeiss Cirrus HD-OCT Model 5000 with AngioPlex) scans were obtained from the optic nerve head of a healthy 22 year old female. Consequently, 3D structural OCT data and OCTA were analysed enabling ODD segmentation and spatial characterization. Results Volumetric analysis of superficial ODD showed a maximal drusen horizontal diameter of 223 µm, maximal vertical diameter of 268 µm, surface area of 6'617 µm2 and volume measurement of 12'875 µm3. The drusen were characterised by a connected network of multiple drusen islands instead of forming a dense mass. Multiple vascular channels with perforating vessels were found across the drusen. Conclusions

	Three-dimensional volume rendering of OCTA scans provided new insight on the spatio-anatomical features of superficial ODD. The new features herein described, namely multilobulated drusen islands and intradrusen channels, may directly contribute to the pathogenic events leading to transient non-embolic visual loss and small vessel occlusion secondary to ODD.
Response to Reviewers:	We are pleased to submit a revised manuscript addressing the points that have been raised. We believe the reviewer's recommendations have allowed us to improve the paper.

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Abstract

Hintergrund

Drusen des Sehnerven (Optic Disc Drusen) stellen sich als verkalkte Ablagerungen dar, die möglicherweise durch Störungen im axonalen Stoffwechsel verursacht werden. Obwohl diese Drusen meist einen milden klinischen Verlauf zeigen und Sehbehinderungen selten sind, können sie mit Gesichtsfelddefekten und Netzhautblutungen assoziiert sein. Optic Disc Drusen können diagnostische Schwierigkeiten verursachen im Vergleich mit anderen Pathologien, die mit kompressiven axonalen Störungen verbunden sind, wie Tumoren des Sehnerven. Daher werden neue bildgebende Modalitäten wie die dreidimensionale Volumendarstellung der Optical Coherence Tomography Angiography (3DOCTA) für eine bessere Visualisierung und das Verständnis von Optic Disc Drusen angewendet.

Material und Methode

Bei einer 22-jährigen gesunden Frau wurden oberflächliche Optic Disc Drusen mit Optical Coherence Tomography Angiographie (OCTA, Zeiss Cirrus HD-OCT Modell 5000 mit AngioPlex) abgebildet. Dreidimensionales Struktur- und OCTA wurden überlagert, die Drusen segmentiert und vermessen.

Resultate

Die oberflächlichen Optic Disc Drusen zeigten einen maximalen horizontalen Durchmesser von 223 Mikrometer, einen maximalen vertikalen Durchmesser von 268 Mikrometer, die Oberfläche betrug 6'617 um2 und die Volumenmessung zeigte 12'875 um3. Die Drusen zeigten keine ganz dichte Masse, sondern stellten sich als ein verbundenes Netzwerk von Druseninseln dar. Mehrere offene Kanäle wurden innerhalb der Drusen gefunden, durch welche Gefäße eindringen konnten.

Schlussfolgerung

Die dreidimensionale Volumendarstellung der Optical Coherence Tomography Angiographie bei Optic Disc Drusen zeigte neue morphologische Merkmale wie multilobulierte Druseninseln und Kanäle innerhalb der Drusen, die für die Netzhautperfusion im Falle einer Gefäßokklusion kritisch sein können.

Background

Optic disc drusen (ODD) are calcified deposits potentially caused by disturbances in axonal metabolism. The clinical course and visual impairment of ODD is usually mild, however, significant ocular morbidity may occur such as visual field defects and retinal haemorrhages. Optic disc drusen may pose a diagnostic dilemma and differentiating these from other entities that can lead to similar compressive axonal distress is imperative. We present a novel technique for three-dimensional (3D) characterisation of superficial ODD based on 3D volume rendering of optical coherence tomography angiography (3DOCTA) scans.

Material and methods

Optical coherence tomography (Zeiss Cirrus HD-OCT Model 5000 with AngioPlex) scans were obtained from the optic nerve head of a healthy 22 year old female. Consequently, 3D structural OCT data and OCTA were analysed enabling ODD segmentation and spatial characterization.

Results

Volumetric analysis of superficial ODD showed a maximal drusen horizontal diameter of 223 µm, maximal vertical diameter of 268 µm, surface area of 6'617 μm^2 and volume measurement of 12'875 μm^3. The drusen were characterised by a connected network of multiple drusen islands instead of forming a dense mass. Multiple vascular channels with perforating vessels were found across the drusen.

Conclusions

Three-dimensional volume rendering of OCTA scans provided new insight on the spatio-anatomical features of superficial ODD. The new features herein described, namely multilobulated drusen islands and intradrusen channels, may directly contribute to the pathogenic events leading to transient non-embolic visual loss and small vessel occlusion secondary to ODD.

Schlüsselwörter

Three-dimensional volume rendering - Optical coherence tomography angiography – Optic disc drusen

Key words

Three-dimensional volume rendering - Optical coherence tomography angiography – Optic disc drusen

Introduction

Optic disc drusen (ODD) are acellular deposits composed of mucoproteins, mucopolysaccharides and iron which undergo progressive calcification [1]. The size and number of ODD vary considerably and they can be found at all prelaminar levels. Smaller ODD tend to be located more proximal to the lamina cribrosa [2]. The clinical course of ODD is usually benign, although they can be associated with visual field defects [3-6], retinal haemorrhages [7-9], optic nerve fiber compression and partial optic nerve atrophy, and juxtapapillary retinal scarring [2]. Diagnosis of ODD is usually based on funduscopic appearance, ultrasonography and fundus autofluorescence. Visual field testing or spectral domain optical coherence tomography (SDOCT) [10-13] may also be of utility. In SDOCT, ophthalmoscopically visible ODD appear as multiple lumps mostly inside the disc with highly reflective borders and internal spaces. Buried ODD appear as a C-shaped mass outside the disc with relatively less distinct borders [12].

We present a novel technique characterised by 3D volume-rendering of OCTA scans (3DOCTA) of superficial ODD. This approach enhances the diagnostic abilities of non-invasive angiography whilst giving new insight on the spatio-anatomical features and how these integrate with angiographic findings of superficial ODD.

Methods

Our technique was applied to OCT scans obtained in a 22 year old Caucasian female. Informed consent was obtained from her for being included in the study. On ophthalmologic examination, best corrected visual acuity was 20/15 and 20/15 in the right and left eyes, respectively. There was no relative afferent pupillary defect. Intraocular pressure was within normal range and colour vision was normal (Ishihara test plates). The anterior chambers and vitreous were clear in both eyes. Fundus examination revealed bilateral superficial ODD with corresponding hyperautofluorescence on autofluorescence imaging.

Autofluorescence and OCT imaging was performed using the Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany). The following OCT parameters were used:15° scan angle, with a scan area 4.4 mm x 4.4 mm x 1.9 mm, Enhanced Depth Imaging on, 73 B-scans with an interslice distance of 61 μm. Imaging with OCT was averaged for 9 scans using the automatic averaging and tracking feature.

The OCTA measurements (3 mm x 3 mm scan area, 245 x 245 pixel) were performed with the Zeiss Cirrus HD-OCT Model 5000 with AngioPlex (Review software 9.0.0.281, Carl Zeiss Meditec, Jena, Germany). All en-face OCTA cutting planes were exported into a 3D OCTA stack. In addition, all structural OCT en-face images were exported into a 3D structural OCT stack (3DOCT). Both image stacks comprised of structural OCT volume (3DOCT) and flow information volume (3DOCTA), were aligned and overlayed. The spaces occupied by ODD were manually segmented by thresholding of pixel intensity. A threshold from 0 to 70 grey-scale units (scale 0 to 255) enabled delineation and separation of the individual lesions. Image artifact from surrounding vessel shadowing was excluded. After segmentation, volume and surface measurements were performed. Finally, all compartments were integrated into one combined volume of structural OCT, OCTA and segmented drusen to study the topographic relationships between vessels and drusen in 3D.

Results

The clinical diagnosis of ODD was confirmed on autofluorescence imaging. Two large drusen were identified in the nasal superior quadrant of the left optic nerve head (ONH ; Fig. 1).

Segmentation of the drusen revealed a maximal drusen horizontal diameter of 223 μm, maximal vertical diameter of 268 μm, surface area of 6617 μm^2 and volume measurement of 12'875 μm^3. A close relationship of the ODD with the surrounding vessels was identified on 3DOCTA (Fig. 2) which in addition revealed the presence of several notches on the surface of the ODD ("drusen indentations"). In the structural OCT, superficial drusen had a round appearance and appeared hyperreflective with a granular aspect.

On the OCTA, the vessel signal density, though reduced, was not entirely devoid of signal. A fainter signal stemming from small vessels could be detected in the hyporeflective areas occupied by the ODD (Fig. 2B). The drusen appeared as islands encroaching these smaller vessels, forming interconnecting vascular channels ("drusen channels").

Discussion

The use of 3DOCTA enabled the identification of new morphological features and interactions in ODD. This new technique facilitated the diagnosis, visualisation and volumetric characterisation of ODD. In contrast to other imaging methods, namely two-dimensional standard OCT [11, 14, 15] and autofluorescence imaging [13, 16], a much more detailed drusen microanatomy with the presence of multilobulated, interconnected drusen lobes was found on combined three dimensional structural OCT and 3DOCTA. Several drusen were organised into a "drusen cluster", whereas others were singular. A new metric approach was provided to measure not only the vertical and horizontal drusen diameter, but to define single drusen surface and volume as well. Potentially, this technique can guide to a specific "drusen cluster matrix". This could be hepful to document drusen's state of equilibrium or express characteristics for drusen dynamics, e.g. fusing of drusen into a cluster. Distinct parameters can be used to monitor the interconnections with other clusters and to classify the clusters and lobules which in turn could be used to document growth and assess mechanical properties. The ability to visualise and perform volumetric and surface measurements in ODD serves as a potential diagnostic and follow-up tool. It may also provide new insight on the pathogenic mechanisms of ODD-related ischaemic events such as retinal occlusion, choroidal neovascularisation [17-19], non-arteritic ischaemic optic neuropathy and peripapillary subretinal haemorrhages [7, 20-22].

Our method revealed another interesting finding. ODD are not a compact circumscribed mass but show several openings ("drusen channels"), through which persisting vessels penetrate (Fig. 3). Calcification of ODD and aggregation formation may potentially contribute to obstruction of the capillary network with consecutive anatomical and functional damage of the retinal nerve fiber layer (RNFL) [23]. It may be a seemingly simple question of what governs and adjusts the geometry of these drusen channels. However, it may be a challenge to develop new morphodynamic models that should be addressed by future research. Implementation of this technique in clinical practice will depend on further temporal analysis of ODD.

In this patient, the ODD showed a very close relationship to the ONH vessels. Arguably, depending on the nature and consistency of the ODD material, the elasticity of the surrounding vessels could be restricted or endovascular changes such as inflammatory effects originated on the drusen surface could be triggered [2] which could lead to a transient or permanent restriction of the vessel perfusion.

There are several limitations to our study. Only superficial drusen were examined and the number of drusen was too low for us to extrapolate our findings to all superficial ODD. The segmentation of the drusen was performed manually with threshold filtering which may lead to artifacts depending on the levels of the threshold and the speckle noise signal. Furthermore, a general accepted threshold level is not defined yet. As OCTA is based on the motion contrast to show blood flow, the visualisation of the vessel singal may be limited beacuse of artifacts due to OCT image aquisition, eye motion, or image processing [24].

This study describes the first use of a new imaging technique, 3DOCTA, applied to superficial ODD. This technique enabled the characterisation of new morphological features of superficial ODD which, to the best of our knowledge, had never been reported. This technique may provide new insight on the pathogenic mechanisms associated with symptomatic ODD.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5).

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Figures

Fig. 1. Fundus imaging of optic disc drusen (ODD) in a 22 year old healthy female. (A) Scanning laser ophthalmoscopy scan of the right optic nerve shows an elevated optic disc with no features of optic disc edema. Multiple, pinpoint-like lesions are seen in the nasal superior quadrant. (B) Corresponding autofluorescence scan of the right eye showing hyperautofluorescence and confirming the diagnosis of ODD.

Fig. 2. Image processing for three-dimensional OCT volume rendering of optical coherence tomography angiography (3DOCTA). (A) En-face-view of optic disc drusen (ODD) (arrow) which demonstrates a hyperreflective area between two hyporeflective vessels (arrow head). (B) Corresponding en-face optical coherence tomography angiography (OCTA) scan of the optic disc depicted in (A) at an identical level. In the area of superficial ODD, an ovaloid area of poor signal is seen (arrow). Minor signals are detected inside the ovoid space. The two hyporeflective vessels around the drusen appear to be pushed outwards. Larger optic disc vessels are separated from smaller vessels by their caliber (arrow heads). (C) 3DOCTA of the same eye shows an elevated vascular network which is a typical feature of ODD. (D) En-face 3D volume rendering shows à signal void area of drusen with visualisation of the white image background. Clearly, the adjacent large vessels (arrow head) are dislocated by the drusen. (E) Drusen are not depicted in the 3D volume rendering of structural OCT. The white spot reflects condensation of posterior vitreous. (F) Combined volume rendering of structural and OCTA of the same optic disc.

Fig. 3. Combined volume rendering optical coherence tomography (OCTA) and segmented optic disc drusen (ODD). (A) Two drusen are visible on the surface of optic disc OCTA (arrows). Smaller, persisting vessels are seen within the ODD, corresponding to the granular OCTA signals in Fig. 2B. Larger vessels wind around the ODD (arrow head). (B) Same volumetric analysis as in (A) in a more posterior cutting plane demonstrates that the ODD are not a uniform corpuscle, but are composed of at least four islands of interconnected extravascular material. (C) After segmentation, the ODD are shown to consist of several smaller lobules partly connected by fine bridges, contrary to their appearance on autofluorescence as à dense compact mass (Fig. 1B). (D) Magnification of the upper left ODD in (C). 3D volume rendering enabled the identification of small openings from within the ODD through which persisting vessels emerge ("drusen channels", arrow head). The surface of the ODD is irregular and several notches are visible ("drusen indentations", arrows).

Figure

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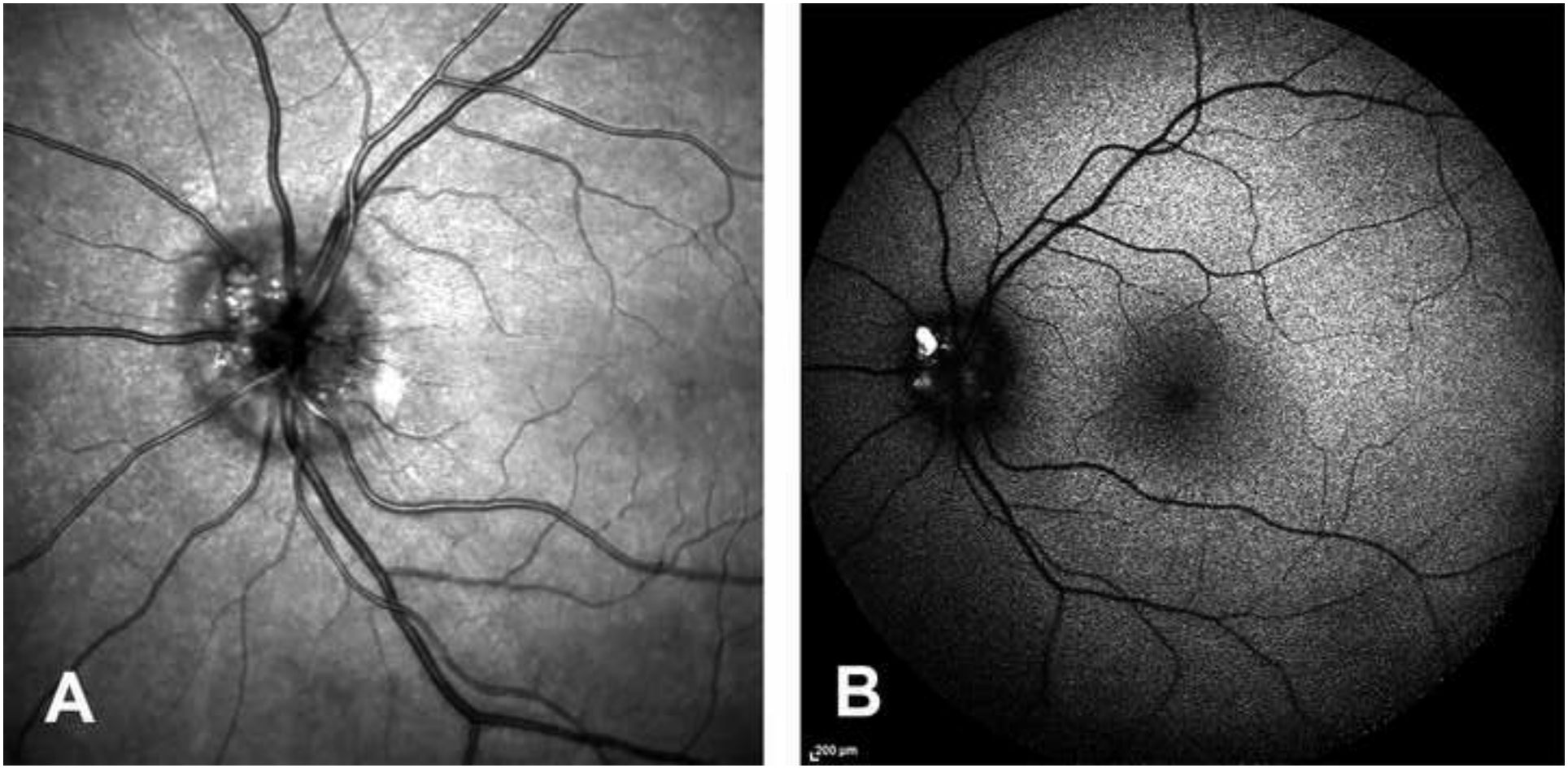

Figure

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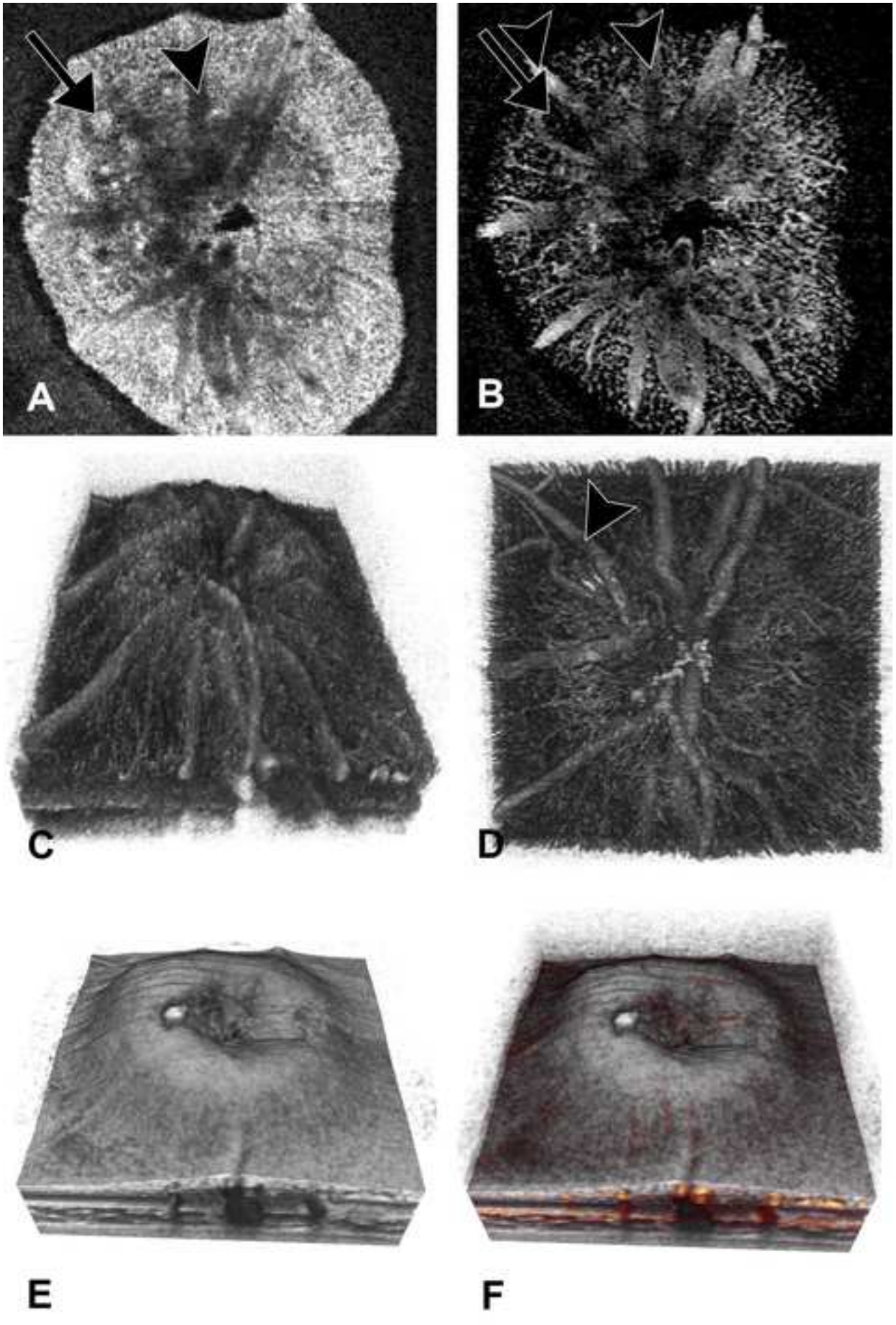

Figure

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