

OCT Angiography for the Evaluation of Wet Age Related Macular Degeneration

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Abstract

Purpose: To highlight the role of optical coherence tomography angiography (OCTA), a relatively new investigative modality, in the evaluation of age related macular degeneration (AMD).

Methods: To evaluate the above mentioned item based on recently published data.

Results: OCTA proves to be a safer investigative tool as compared to the traditional fluorescein angiography (FFA) and of superior benefit in better delineation of the pathological changes in AMD.

Conclusion: OCT angiography may be clinically useful to evaluate the CNV activity and response to treatment as well as to differentiate the various types of CNV in wet AMD.

Keywords: OCTA; AMD; FFA

Introduction

How is the OCTA done for AMD

Heyex Software Version 1.9.201.0, Heidelberg Engineering, Heidelberg, Germany) provided an automated segmentation algorithm for retinal and choroidal layers.

Two automatically segmented lines, separated by 30 μ , and horizontal or shaped on the RPE or Bruch's membrane profile, were manually fine-tuned to be located immediately above the RPE and then moved progressively deeper in 30 μ steps, up to the choroidal-scleral interface. This allowed the analysis of all the structures included in a 30- μ thick "slice of tissue" in an en-face visualization.

The 30- μ thickness was established for each C-scan because of its ability to show all the coplanar structures in a given section while avoiding the risk of superimposition that is typical of thicker sections. The possibility to have an RPE-shaped C-scan section enables clear visualization of the neovascular tissue that is attached to the back surface of the RPE.

The importance of starting the assessment above the RPE is due to the fact that there are no vascular structures in healthy eyes at this level. Therefore, OCTA is not expected to detect blood flow at the level of the outer retinal layers. The examiners therefore evaluated a series of images per patient (i.e., serial sections) in order to carefully analyze all the retinal and choroidal tissue that were present between 30 μ above the RPE and the choroidal-scleral interface. In this way, each CNV feature was identified, when present in a given C-scan, even if it was not visible in any deeper or more superficial section [1].

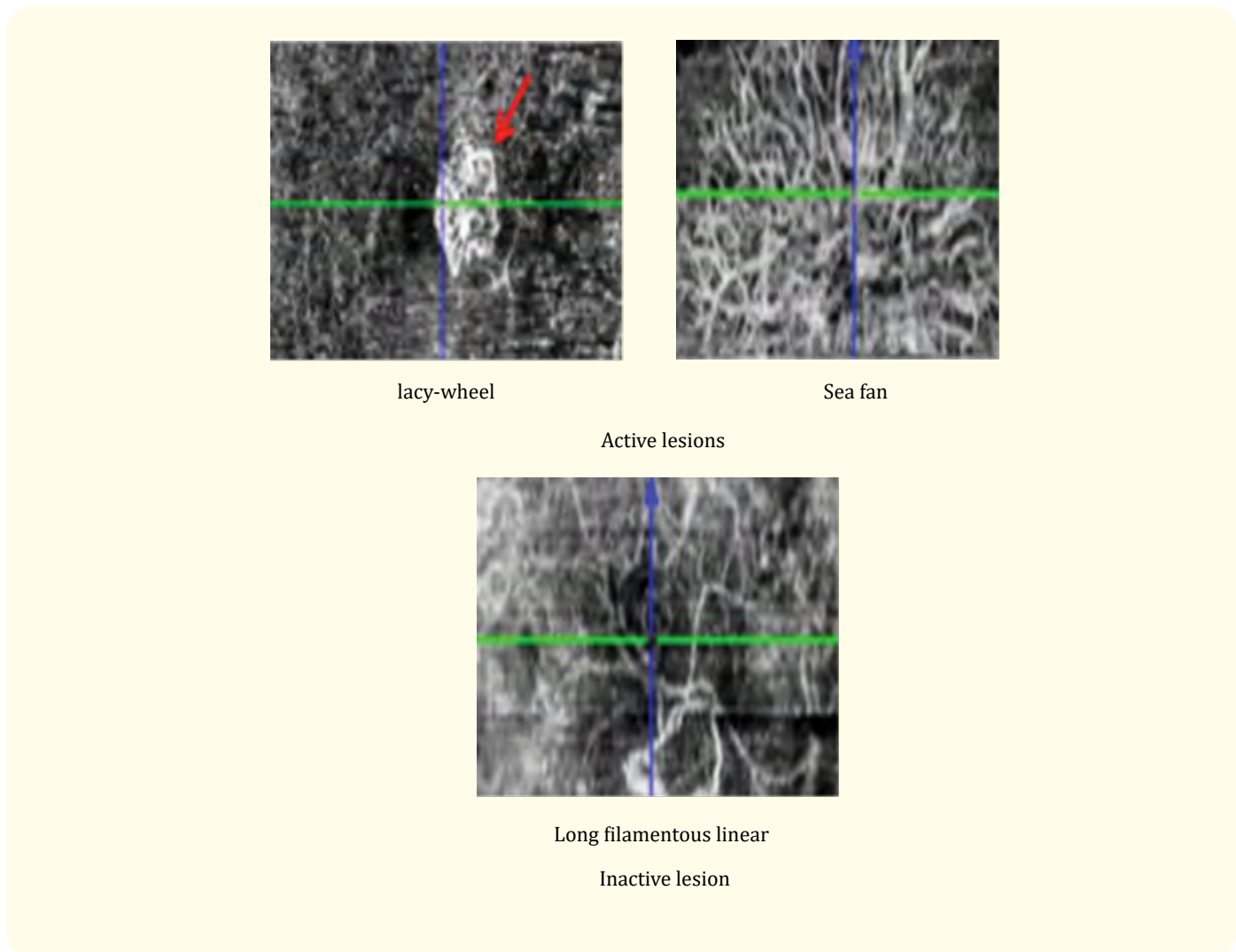
OCTA in wet AMD

According to OCTA lesions, AMD was classified into 2 patterns; pattern I requiring treatment and pattern II not requiring treatment.

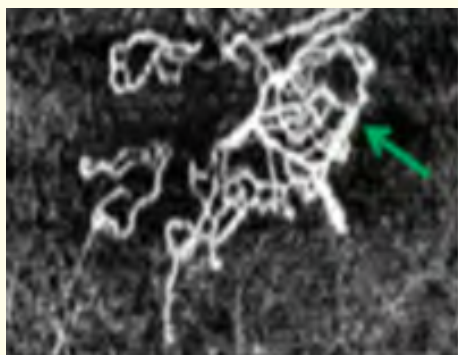
Pattern I lesions

A lesion was assessed as Pattern I, requiring treatment, if it showed all or at least three of the following five features: [2-4]

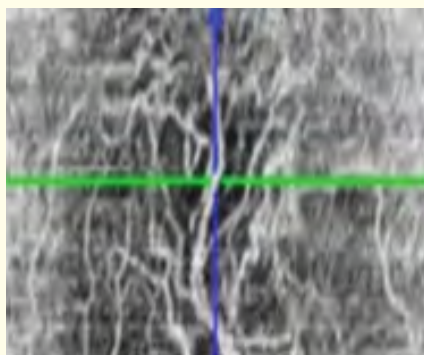
1) Shape, a well-defined (lacy-wheel or sea-fan shaped) CNV lesion in contrast to one with long filamentous linear vessels.



2) Branching, numerous tiny capillaries, typical of a recent lesion, in contrast to rare large mature vessels, typical of a mature one.

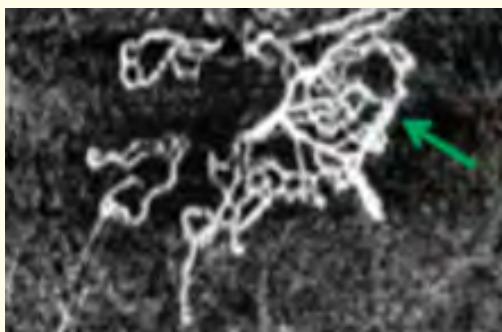


numerous tiny capillaries
Active recent lesion

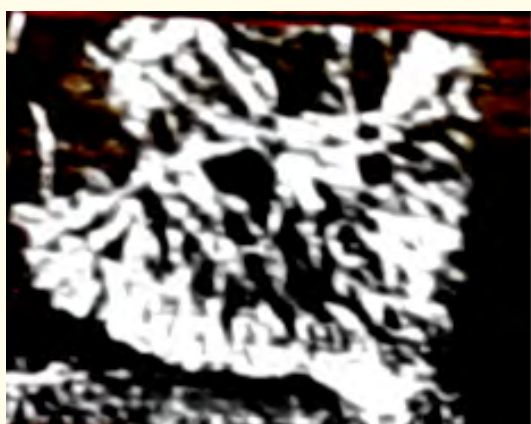


rare large mature vessels
Inactive mature vessels

3) The presence of anastomoses and loops.



4) Morphology of the vessel termini, assessing the presence of a peripheral arcade in contrast to a “dead tree” appearance.

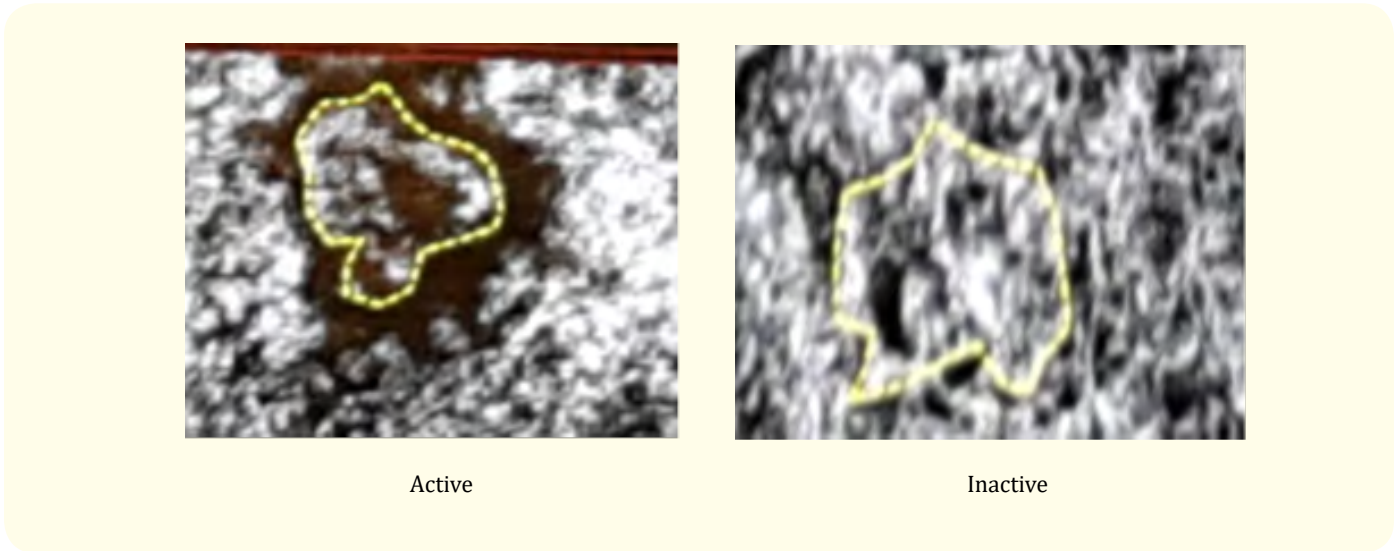


peripheral arcade
Active



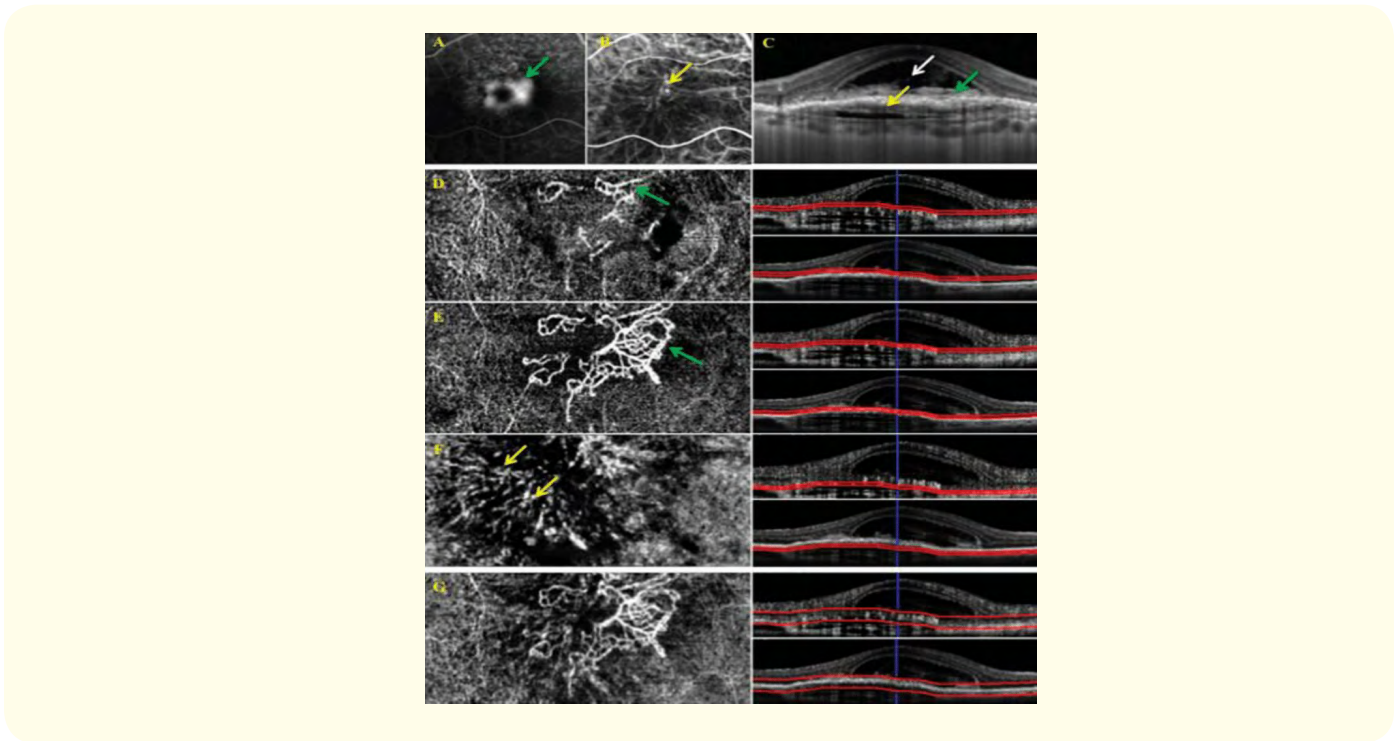
“dead tree” appearance
Inactive

5) Presence of a perilesional hypointense halo, considered as regions of choriocapillaris alteration, either corresponding to flow impairment, steal or localized atrophy.



Pattern II lesions

- A CNV lesion was considered as Pattern II, not requiring treatment, if it showed less than three of the previously reported OCTA features.
- These OCTA criteria were selected after considering the previously reported findings based on histopathology, FA and ICGA angiography, OCT, and the recently introduced OCTA [5-11].



A–G. Traditional multimodal imaging (A–C.) and OCTA (D–G.) in AMD.

- A. Fluorescein angiography in the early venous phase shows the presence of leakage in macular area (green arrow).
- B. On indocyanine green angiography is clearly visible, a wide PED associated with an extensive Type I (sub-RPE) neovascular network (yellow arrow).
- C. The OCT shows the presence of subretinal fluid (white arrow), a hyperreflective band above the RPE (green arrow), probably referred to a Type II (pre-RPE) CNV, and a wide fibrovascular PED (yellow arrow), probably representing the Type I component of a mixed (Type I and II) CNV.
- D. Optical coherence tomography angiography C-scan, 30-mm thick, modeled on the RPE profile and taken at the level of the outer nuclear layer (B-scan images, both in angiographic and conventional mode, are shown as reference on the right). There is the initial visualization of a vascular hyperintense decorrelation signal due to a Type II neovascular lesion: Large mature vessels, associated with tiny ones, are visible.
- E. On the following C-scan, taken immediately above the RPE, the entire extension of a sea-fan Type II CNV (green arrow) is shown: Large mature vessels, branching into smaller ones toward the periphery, anastomoses, and peripheral arcades, are visible.
- F. On a deeper C-scan section, taken inside the PED an extensive Type I neovascular network is shown (yellow arrows).
- G. Optical coherence tomography angiography C-scan thick section: this image is voluntarily obtained from a thick section including all the mixed Type I and II CNV. Tiny details are less contrasted and sometimes not visible, as well as the entire extension, which seems substantially reduced compared with the image shown above. Moreover, there is a clear prevalence of the Type II component on the type I, in terms of visibility [4].

Value of OCTA in the follow up of treatment response of wet AMD CNV to anti VEGF treatment

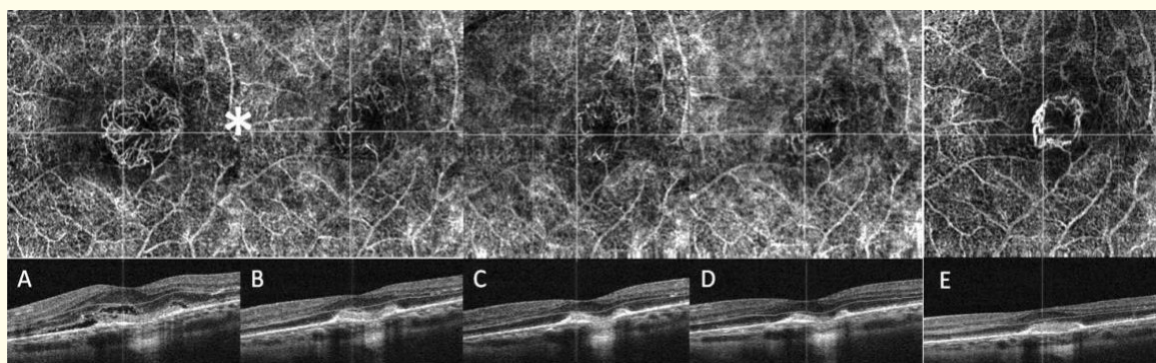
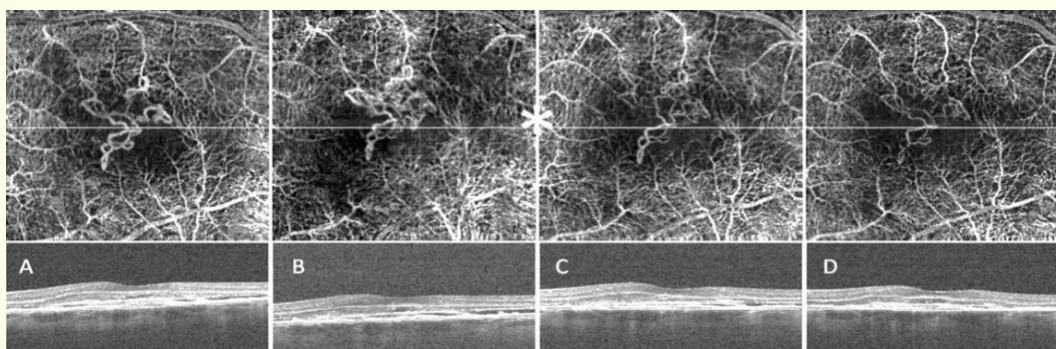


Figure 7: Optical coherence tomography-angiography study of type 2 naive choroidal neovascularization early response after treatment.

Optical coherence tomography–angiography study of type 2 naive choroidal neovascularization early response after treatment.

- First cycle after treatment of naive CNV.
- A. **Before treatment**, OCT-A shows a roundish CNV with no evident central afferent vessel but dense fine irregular capillaries arborescence. A dark choriocapillaris area is seen around CNV.
- First treatment, first cycle: *Intravitreal injection.
- B. **Twenty-four hours after treatment**: decrease of visible vessels in number and density, with apparent vessel fragmentation. Choroidal neovascularization area decreased. Pruning of thinner anastomoses and loss of smaller vessels are observable. The network density decreases and central area seems empty. Residual flow is uneven and more visible close to the afferent trunk.
- C. **Ten days after injection**: maximum CNV decrease, with area center apparently empty without vascular circulation.
- D. **Fifteen days after injection**: same CNV decrease, with area center empty without vascular circulation.
- E. **Thirty-two days after injection**: Reproliferation vessels appear in the periphery of a circular area. These vessels could be the same vessels that were collapsed, but their caliber is much greater, with loss of smaller vessels. The CNV area is smaller [4].



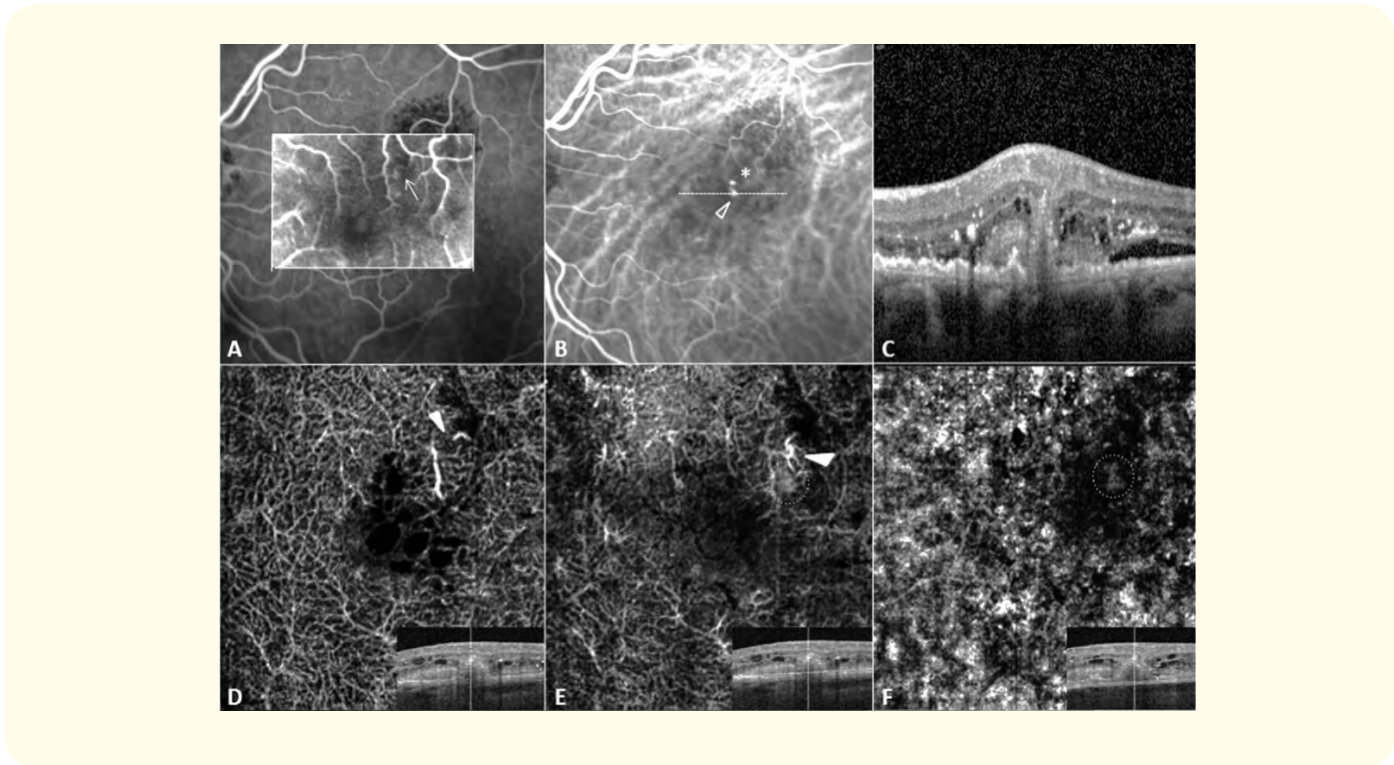
- **Sixth cycle, recurrence, new vessels sprouting, new treatment.** After the sixth injection, the evolution is similar to other cycles. Tangled pattern CNV.
- A. The CNV area is smaller than 1 year before. Vessels are rare and thick with a tangled pattern. They show an increased caliber and increased flow.
- B. **Recurrence 66 days after sixth injection**, patient reports a sudden vision decrease with metamorphopsia. Optical coherence tomography–angiography shows a recent new sprouting of thin capillaries at the superior extremity of the residual arterIALIZED vascular net.
- ***Intravitreal injection.**

- **C. Twenty-four hours after new treatment:** The seventh injection causes the almost complete regression of the new vessels sprouting in a few hours. Network density and area decrease again, highlighting some of the same major preexisting vessels.
- **D. Ten days after seventh injection.** Total regression of the new vessels sprouting. Network density and area are back to situation preexisting the recurrence. We see the same preexisting vessels [4].

OCTA in the evaluation of type III CNV in wet AMD

- The Type 3 lesion has been described as early capillary proliferation within the retina in the perifoveal area that may subsequently progress to infiltrate the RPE becoming associated with an underlying serous PED. Serous PED has been associated with breakdown of the RPE barrier and leakage from the neovascular lesion, without communication with the choroid [12-14].
- Histopathologic studies have revealed a plexus of blood vessels in the outer retina in Type 3 NV emanating from the deep retinal capillary plexus [13].
- On the en face images, the neovascular complexes appeared as small tufts of bright, high-flow tiny vessels with curvilinear morphology located in the outer retinal layers, which distinguished them from the surrounding capillaries [15].

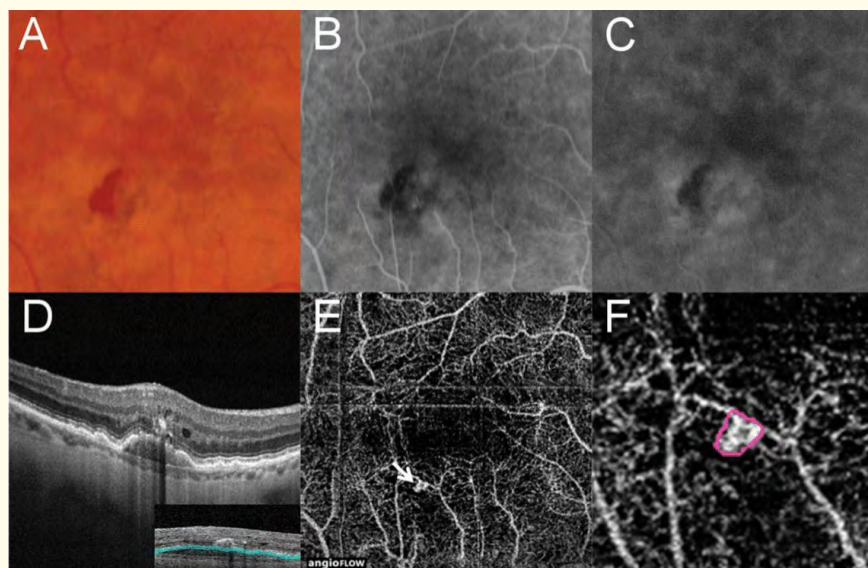
Early Type III neovascularization



- A. Early frames of FA show a small area of hyperfluorescence superior to the fovea, generated by an arteriole and venule (enlarged view, arrow).

- B. **Indocyanine green angiography** early frames demonstrate the connection between the arteriole (asterisk) and venule (open arrowhead), as two round hyperfluorescent lesions superior to the foveal avascular zone.
- C. **Optical coherence tomography (OCT)** guided by ICGA demonstrated a hyperreflective intraretinal complex, emanating from the deep capillary plexus, apparently connected with the sub-RPE space, characterized by intraretinal and subretinal exudation.
- **D-F. 2-mm · 2-mm OCTA images and corresponding OCT B-scan.**
- D. Optical coherence tomography angiography deep capillary plexus segmentation showing a high-flow third order vessel descending toward the outer retinal layers (arrowhead).
- E. A tuft-shaped high-flow lesion appears in the outer retinal layers, characterized by a retinal-retinal anastomosis and abutting into the sub-RPE space (arrowhead).
- F. The choriocapillaris segmentation reveals the tuft-shaped lesion apparently connected to a deeper small clew-like lesion (dotted circle in E and F) [16].

Small type III neovascularization

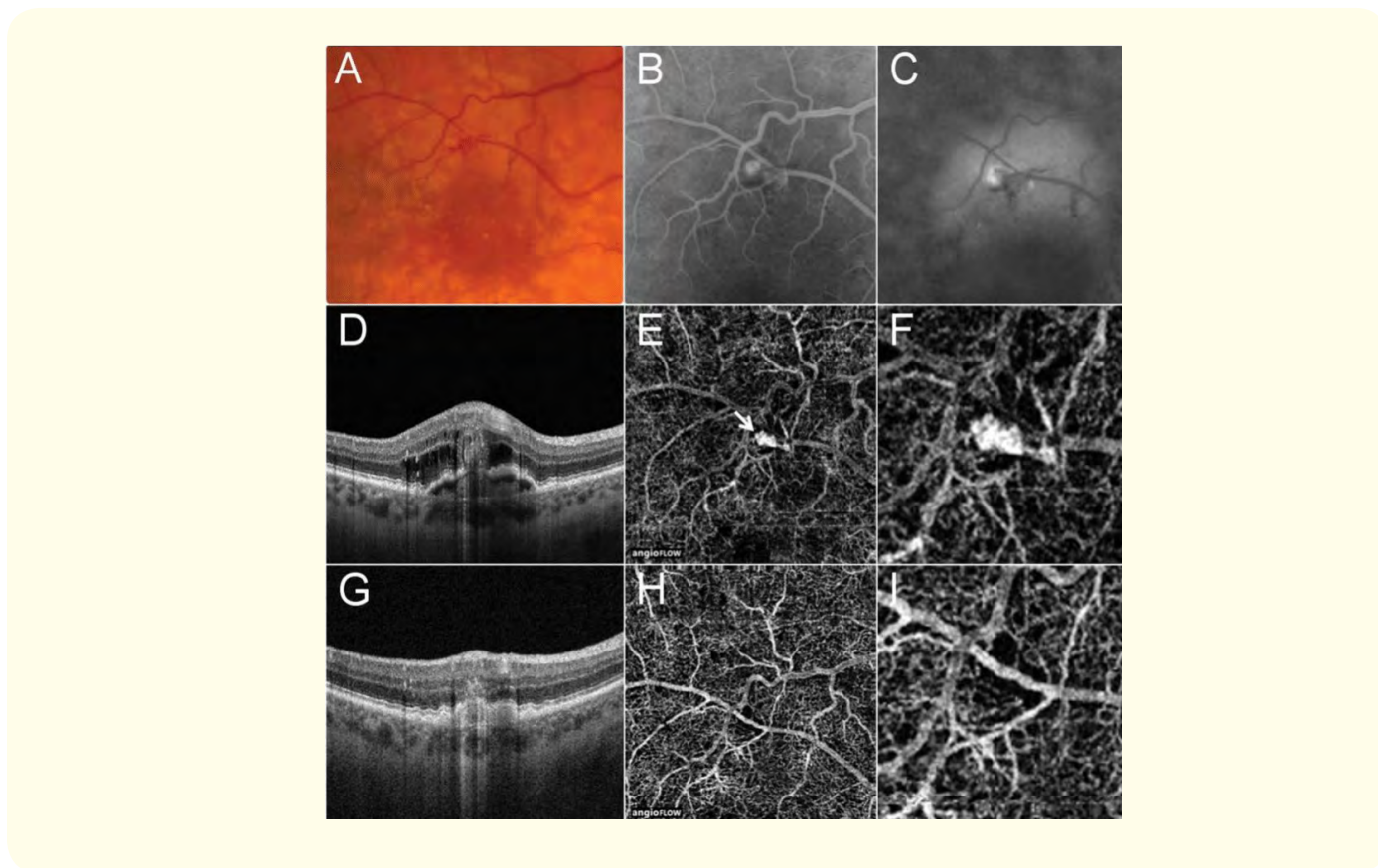


- **Multimodal imaging of a very small Type 3 neovascular lesion in AMD.**
- A. Magnified color fundus photograph. Note the intraretinal hemorrhage associated with the Type 3 lesion.
- B and C. Fluorescein angiography, early (B) and late (C) phase, shows blocked fluorescence from the hemorrhage and pooling within the adjacent drusenoid PED. The Type 3 lesion is not clearly identifiable with angiography.
- D. Spectral domain OCT image. Note the drusenoid PED, the intraretinal fluid, and the hyperreflective density (consistent with

Type 3 NV) located in the outer nuclear layer directly over the PED. The B-scan registered with the OCTA scan in the bottom right corner of panel D shows the segmentation lines. In this case, the upper and lower boundaries of the slab were the RPE and the RPE with an offset of 29 mm; the slab thickness was 29 mm.

- E. 3-mm · 3-mm OCTA en face projection image shows a small but distinct Type 3 neovascular lesion (arrow).
- F. High magnification of E. Note the morphology of the Type 3 neovascular complex with OCTA showing a small round complex with a cluster of curvilinear small caliber vessels, which was not visible with conventional angiography [15].

Response of type III neovascularization to anti VEGF treatment as evaluated by OCTA



Type 3 neovascular complex in AMD before and after intravitreal injection of aflibercept.

- A. Color fundus photograph. Note the intraretinal hemorrhage superior to the fovea.
- B and C. Fluorescein angiography, early (B) and late (C) phase, shows blocked fluorescence from the heme, an adjacent small hotspot corresponding to the Type 3 neovascular lesion, and late pooling into the mixed serous and drusenoid retinal PED.
- D. Spectral domain OCT imaging before treatment shows a mixed serous and drusenoid PED associated with intraretinal fluid,

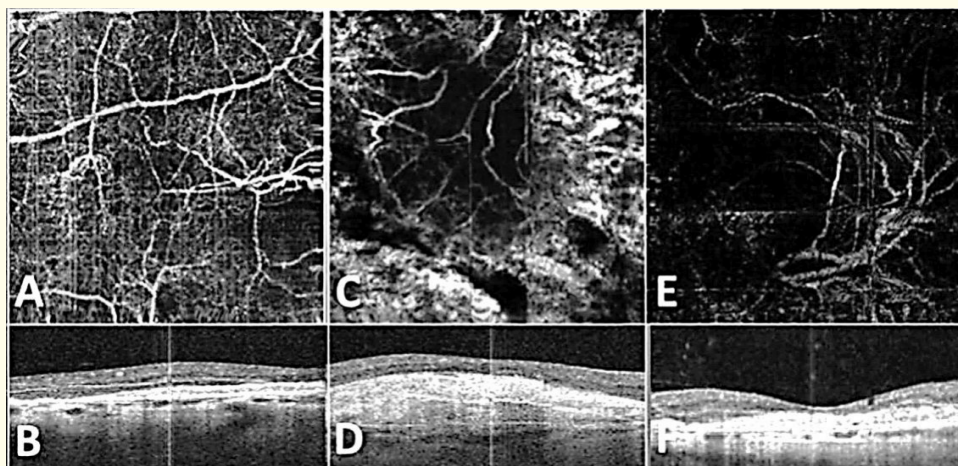
and a hyperreflective density that corresponds to the Type 3 membrane and is located in the outer nuclear layer and is communicating through the RPE.

- G. Spectral domain OCT imaging 7 weeks after treatment with aflibercept shows reduction in the PED and resolution of the intraretinal fluid, a smaller hyperreflective density located in the outer nuclear layer, and atrophy of the outer retina.
- E and H. 3-mm · 3-mm OCTA en face projection images shows the Type 3 neovascular lesion (arrow) before (E) and after (H) treatment.
- F and I. High magnification of E and H. Note the morphology of the Type 3 neovascular complex with OCTA, which shows a small bright ellipsoid lesion with a cluster of curvilinear small caliber vessels (E and F). The characteristic neovascular complex is no longer visible after a single intravitreal aflibercept injection (H and I) [15].

Octa Features of Subretinal Fibrosis in Age-Related Macular Degeneration

- Optical coherence tomography angiography analysis distinguished three features of neovascularization inside a fibrous scar:
- The features could also be grouped in two major phenotypes:
 1. Pruned vascular tree
 2. Blossoming tree (including tangled network and vascular loop).
 3. Also, recognized two dark lesions (large flow voids and dark halo) [17].

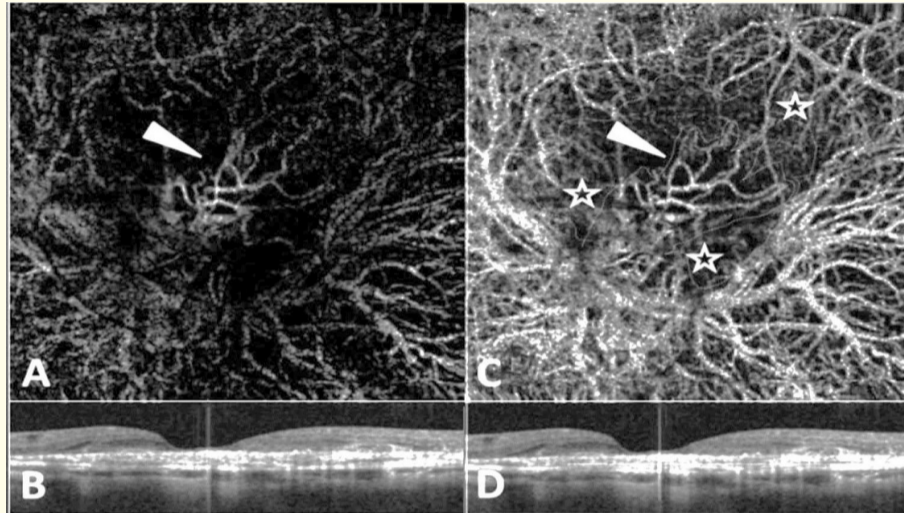
Pruned tree pattern



- Pruned vascular tree pattern refers essentially to a neovascular network with irregular, filamentous flow, consisting only of important vessels, with no thinner capillaries visible with moderately high, irregular flow (A, C, E).
- The corresponding B-scans (B, D, F) show an hyperreflective fibrous scars of various sizes.

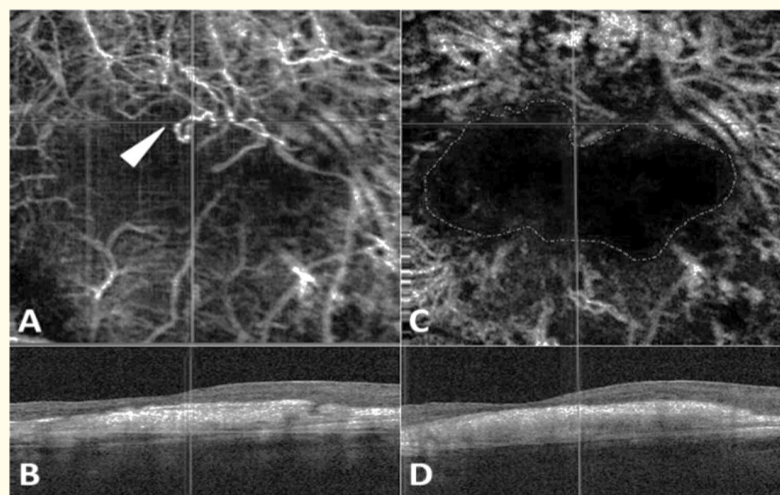
- Note that (A and C) the presence of a high flow neovascular network composed by a central feeder vessel and emerging large vessels, with no thin branches visible and surrounded by a darker masking area.
- E. Shows large, centrifugal, high flow vessels in the OCT-A segmentation corresponding to the outer retinal layers [17].

Tangled network pattern



- Tangled network is characterized by an abnormal, high flow, frequently interlacing vascular network, in the segmentation corresponding to the fibrotic scar.
- OCTA images of the outer retinal segmentation and choriocapillaris segmentation (A and C, respectively), and corresponding B-scan (B and D).
- The tangled neovascular network (arrowhead) appears as high flow structure, comprising thin emerging branches and many collateral branches to the surrounding vessels (stars). Note the surrounding dark area, which could correspond to a hypoperfused area (dotted green line) surrounding still active CNV [17].

Vascular loop



- Vascular loop consists of a small, high flow convoluted network in the segmentation corresponding to the fibrotic scar.
- OCTA image of the outer retinal segmentation (A) and corresponding B-scan (B). Note a high flow, small vascular loop (white arrowhead) on the border of the fibrotic scar.
- OCTA image in the choriocapillaris segmentation (C) and corresponding B-scan (D) show the large flow void [=vacuum] (dotted yellow line) [17].

Subretinal fibrosis is a consequence of complex tissue repair mechanisms, comprising sequences such as angiogenesis, formation of granulation tissue, and remodeling by connective tissue [18]. Connective tissue growth factor is one of the key players in the pathway leading to fibrosis [19-20].

All in all, the pathogenic sequence of subretinal fibrosis, even if partially understood, seems to consist of a leucocytary exudation by the highly permeable new vessels, which initiates the inflammation process, stimulating glial proliferation and ultimately generating subretinal fibrosis [21-23].

Conclusion

OCT angiography may be clinically useful to evaluate the CNV activity and response to treatment as well as to differentiate the various types of CNV in wet AMD.

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