OCT INTERPRETATION

Clinical Analysis and Interpretation of OCT Characteristics in AMD Comparison with Angiography

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Introduction

Optical coherence tomography (OCT) imaging has been widely accepted by ophthalmologists as an attractive imaging modality. It not only provides a wealth of information, but it is also non-invasive and easy to perform.

In particular, OCT can provide an overview of the neurosensory retina, retinal pigment epithelium (RPE), Bruch's membrane, and choroid in age-related macular degeneration (AMD)

For example, the presence of **intraretinal fluid, subretinal fluid,** or fluid underneath the RPE may indicate *abnormal leakage* derived from choroidal neovascularization.

The evaluation of the leakage can be precisely quantified, which is useful for monitoring progression of disease or response to treatment.

Although retinal thickness is a precise and informative measurement, OCT can provide much more additional insight.

Detailed examination of changes observed on cross-sectional images of the macular region allows:

- *Analysis* of each layer of the neurosensory retina, retinal pigment epithelium (RPE), Bruch's membrane, and choroid to establish a **definitive diagnosis**.
- *The interpretation of OCT signs* is based on recognizing patterns of abnormalities induced by various lesions and their complications.

For each OCT image, the following should be considered:

- **Alterations of normal structures:**
  - There can be changes in the different tissue layers: the choroid, Bruch's membrane, RPE, neurosensory retina, or in the potential **spaces** between these layers.
- **Additional structures**:
  Pathologic lesions have characteristic variations of reflectivity, which allow their identification. For example, drusen, choroidal neovascularization, hemorrhage, fluid accumulation, pigment deposits, and exudates all appear distinct on OCT.
- **Grouping of the various signs** induced by the combination of these different alterations allows a **more precise diagnosis** of the *type and stage of AMD*, and particularly, the etiology for vision loss, such as choroidal neovascularization or progression to atrophy.
- The **polymorphic natural history** and response to treatment accounts for the different and numerous clinical forms of AMD that should be identified in order to guide treatment.

Besides OCT, *traditional angiography* is still essential to identify choroidal neovascularization and localize it in relation to the fovea.

Fluorescein angiography (FA) is the gold standard for detecting classic choroidal neovascularization (CNV), while **indocyanine green angiography (ICG)** helps visualize occult CNV, and the almost always associated pigment epithelial detachments (PED).

Although OCT cannot directly illustrate choroidal neovascularization like angiography does, it can show highly suggestive **indirect signs**.

An advantage of OCT examination over angiography for the patient is that it does not require an intravenous injection of dye.

Recent developments in imaging systems allow simultaneous display of FA, ICG, and OCT.

This remarkable progress allows exact spatial correlation of angiography with OCT, which helps draw more effective conclusions.

Interpretation of an OCT Image

Interpretation of OCT images must therefore avoid assumptions based on a global, intuitive approach. The examiner should proceed systematically in each case as if completing a reading chart or grid.

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- **First step:**

The first step is to identify and follow the ***RPE* band,** looking for:

- Irregularities, thickening, fragmentation, effraction, disruption, or shadowing.

The RPE must also be examined for:

- Potential separation of the RPE from Bruch's membrane, which then becomes visible and distinct from the RPE.

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Posterior to the RPE band:

The analysis continues by studying variations behind the RPE, essentially looking for:

- The presence of **hyper-reflectivity** extending posteriorly throughout the choroid, suggesting atrophy, or on the other hand,
- **Hypo-reflectivity, which** suggests shadowing derived from overlying structures.

Anterior to the RPE band:

Retinal thickness, anterior to the RPE, must then be analyzed for:

- The presence of *cavities* or *deposits*, and
- Analysis of *the neurosensory retinal layers*, membranes, and vitreous.

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Spectral-Domain OCT

Spectral-Domain OCT (SD-OCT) has transformed analysis of the **external layers of the retina**.

This new technology allows:

- High-resolution visualization of *retinal layers*, and
- Easy distinction of the *interfaces* between the various structures.

This can be obtained as a result of noise reduction and enhanced contrast.

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This **separate analysis** of the structures and their various abnormalities observed on an OCT section is clearly *schematic and somewhat arbitrary*.

There are virtually no cases in which a pathological lesion affects only one layer or only one tissue.

Therefore, interpretation of localized lesions must also take changes in adjacent structures into account.

I. Retinal Pigment Epithelium

In the Normal Eye

Time-Domain OCT

In Time-Domain OCT, the RPE appears to be clearly visible, as it is a distinct and hyper-reflective structure compared to adjacent structures.

However, this structure actually corresponds to the RPE-Bruch's membrane-choriocapillaris *complex* that is difficult to dissociate, except in pathological conditions.

Spectral-Domain OCT

This technology allows much more detailed analysis, but paradoxically, leaves a larger number of unknowns.

- **The retinal pigment epithelium (RPE)** appears to present (according to some authors) not one, but two, distinct hyper-reflective bands separated by a thin hypo-reflective band (**Figures 1 and 2**).

This feature was first observed with ultrahigh-resolution OCT systems.

The *outer hyper-reflective band* appears to correspond to the pigment epithelium cell bodies, but the origin of the *inner band* has not been clearly elucidated.

Some authors consider this inner band to correspond to *Verhoeff's membrane*, composed of tight junctions between pigment epithelial cells.

According to another hypothesis, this inner band corresponds to basal infoldings and apical processes that enclose photoreceptor outer segments.

This feature is only visible with ultrahigh-resolution systems (or systems associated with adaptive optics) and in normal eyes.

These two bands are *more difficult to distinguish* in the presence of pathological changes, which could have a prognostic value.

- **Bruch's membrane (BM)** is usually not visible on OCT in a normal eye.

It is only really visible and distinct when there is a loss of localized adhesion and it is separated from the RPE with a more or less marked elevation of the RPE band, like in a retinal pigment epithelial detachment.

- The **choriocapillaris** remains poorly visualized and its alterations are almost impossible to analyze.

In the future, the use of longer wavelengths in the infrared spectrum will probably allow better visualization of the choroid.

- The **thickness of the RPE** cannot be measured by Time-Domain OCT but can be measured manually by Spectral-Domain OCT.

Different structures **anterior to the RPE** can now be analyzed:

- The **external limiting membrane** (ELM), which is a fused structure corresponding to the alignment of structures between photoreceptors and Müller cells.

- The **interface** (or **junction)** between photoreceptor inner segments and outer segments **(IS/OS).**

Photoreceptor **inner segments** and **outer segments** can therefore be more precisely evaluated by visualization of these hyper-reflective lines and the hypo-reflective zones on either side.

The **distance** between the RPE and the IS/OS interface increases in the foveal region, corresponding to the longer outer segments of cones in this region (**Figures 1 and 2**).

These normal findings can be used to methodically follow the RPE band from the perimacular zone (usually normal) to the central lesion.

NORMAL RETINAL PIGMENT EPITHELIUM AND RETINAL LAYERS RETINIENNES NORMALES

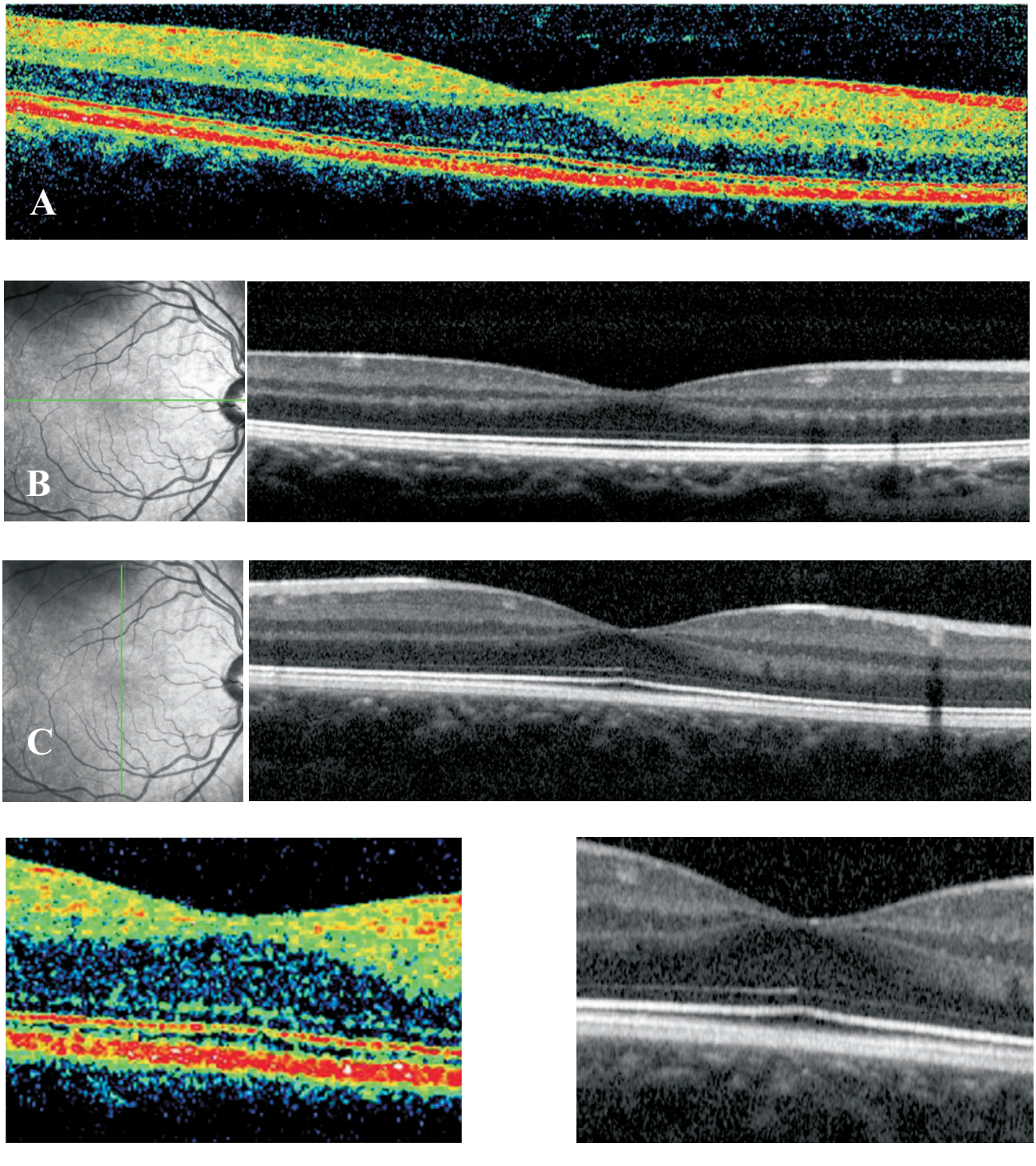
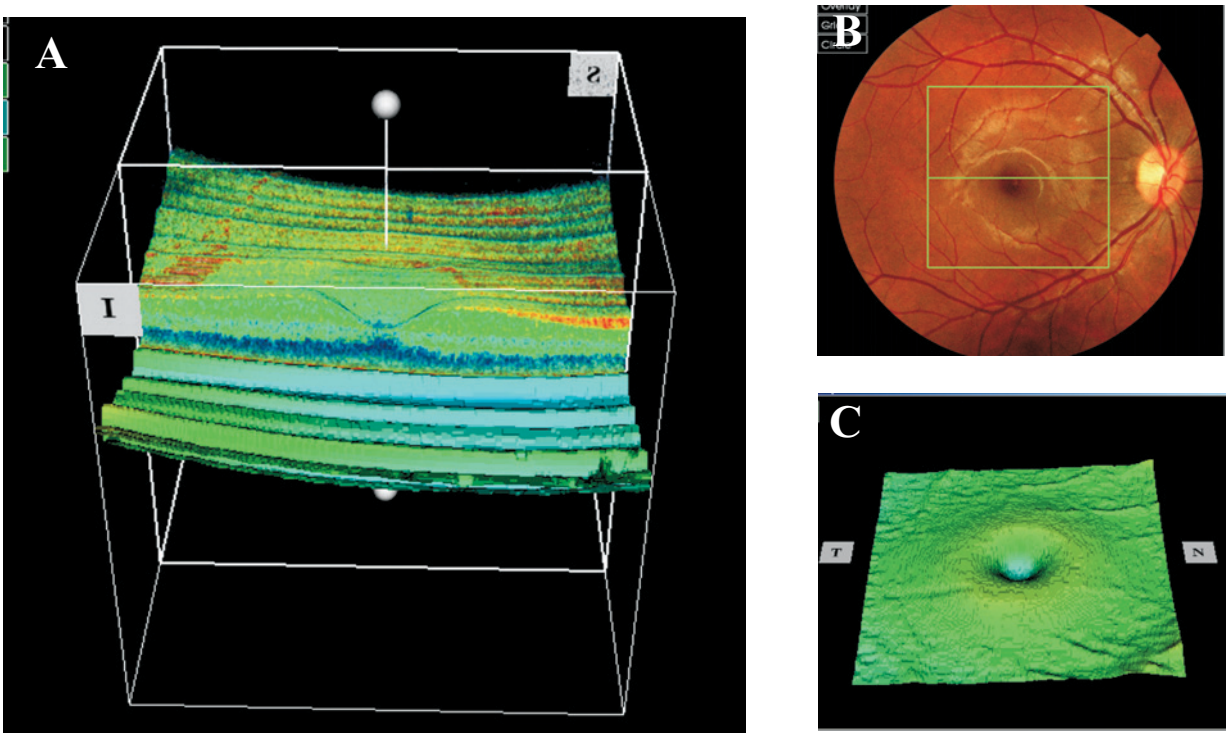


Figure 1: Normal SD-OCT (*Spectralis) section.**
A): Color image. **B** and **C)**: Black and white images at different magnifications.
This section delineates the external limiting membrane, the inner segment/outer segment interface, the retinal pigment epithelium, and the choroid. Two distinct layers in the RPE can be seen.
These images are shown with reference red-free images with a horizontal OCT section (B) and an OCT vertical section (C). Fluorescein angiography and SLO-ICG angiography images can also be selected.

NORMAL RETINAL PIGMENT EPITHELIUM AND RETINAL LAYERS



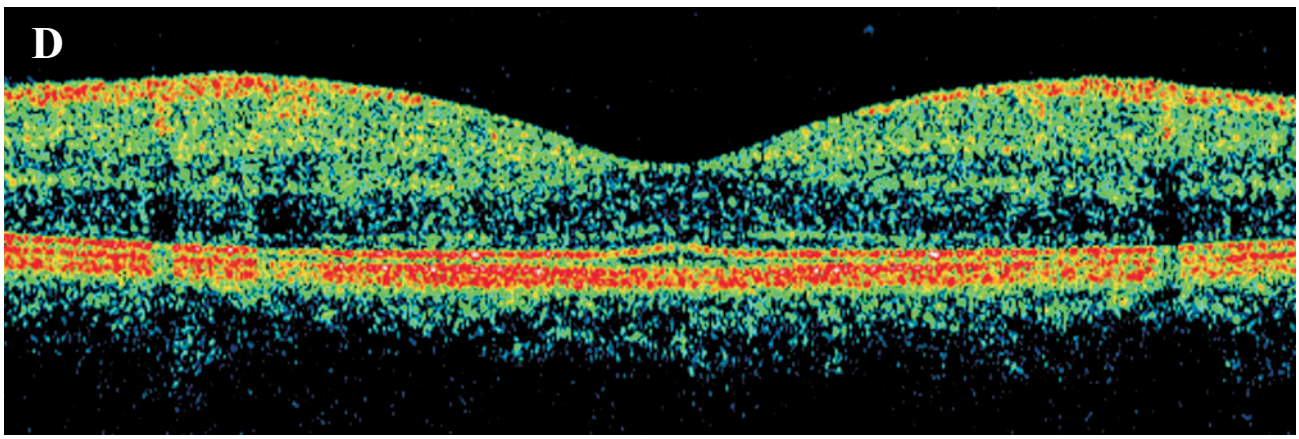


Figure 2: Normal SD-OCT (*Topcon) section.**

A): Volume image with partial segmentation, allowing analysis of the axial cross section (through the center of the fovea) and of the different surfaces.

B): Color reference images showing the zone of examination.

C): False-color image of the retinal surface.

D): Axial section showing the external limiting membrane, the inner segment/outer segment interface, the retinal pigment epithelium, and the choroid.

In Clinical Practice

SD-OCT can be used to detect and evaluate:

- Variations of *thickness*, *contour, irregularities,* and *fragmentation,* which must be distinguished from shadowing artifacts.
- *Detachment* of Bruch's membrane.
- The presence of *abnormal structures* located **anterior** or **posterior** to the RPE.

Each of these abnormalities are usually visible on Time-Domain OCT, but they are demonstrated much better on SD-OCT.

The use of SD-OCT is often able to distinguish more subtle abnormalities, which may not be detectable by other modalities.

Enlarged OCT images are useful to precisely analyze these minute structures, whose physiological role and pathological alterations are so important.

In macular diseases and AMD, lesions are rarely larger than a **20° field,** and SD-OCT magnified images provide satisfactory demonstration of pathological details.

Bruch's Membrane

Bruch's membrane (BM) becomes visible when there is a loss of adhesion between itself and the RPE.

This loss of adhesion is usually due to abnormal exudation from choroidal neovascularization underneath the RPE.

In this context, Bruch's membrane is seen as a very regular, homogeneous, slightly hyper-reflective, and relatively thin line.

This line should be used as the outer limit for retinal thickness measurements (**Figure 3**).

Inner Segment/Outer Segment Interface

The inner segment/outer segment interface (IS/OS) is visible as a hyper-reflective line anterior to the RPE.

There is a dark, hypo-reflective space delineated by the RPE on one side and the IS/OS interface on the other side. This space corresponds to *photoreceptor outer segments.*

Another hypo-reflective space is bordered by the IS/OS interface and the external limiting membrane and corresponds to *photoreceptor inner segments.*

These three boundaries (BM, IS/OS interface, and external limiting membrane) constitute essential landmarks during assessment of AMD (**Figure 4**).

RETINAL PIGMENT EPITHELIUM AND OUTER RETINAL LAYERS

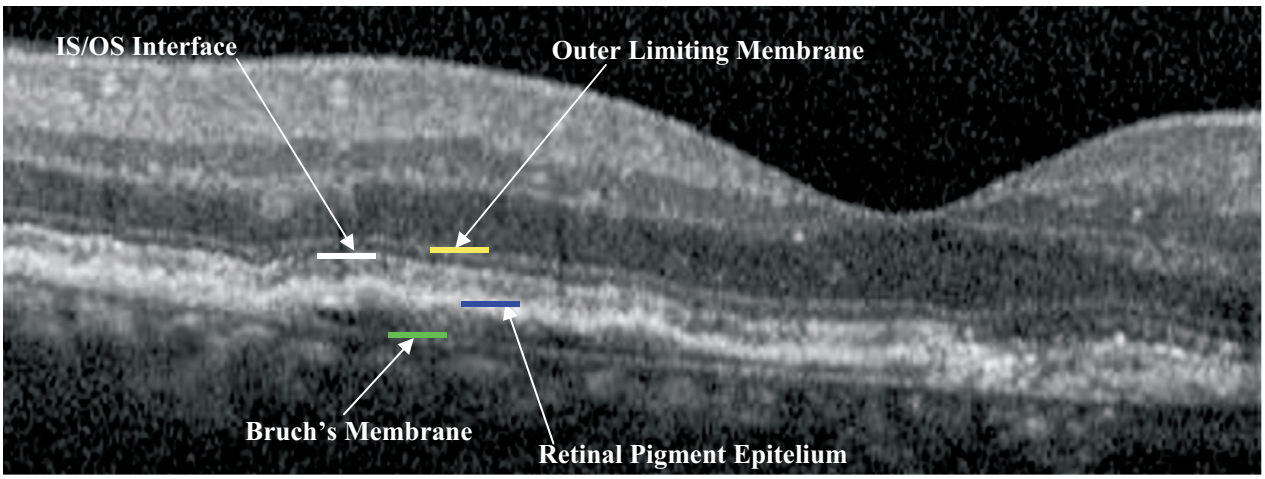


Figure 3: SD-OCT section showing a very limited PED, allowing distinction between the inner segment/outer segment interface, the external limiting membrane, the RPE band, Bruch's membrane, and the choroid (*Spectralis*®).

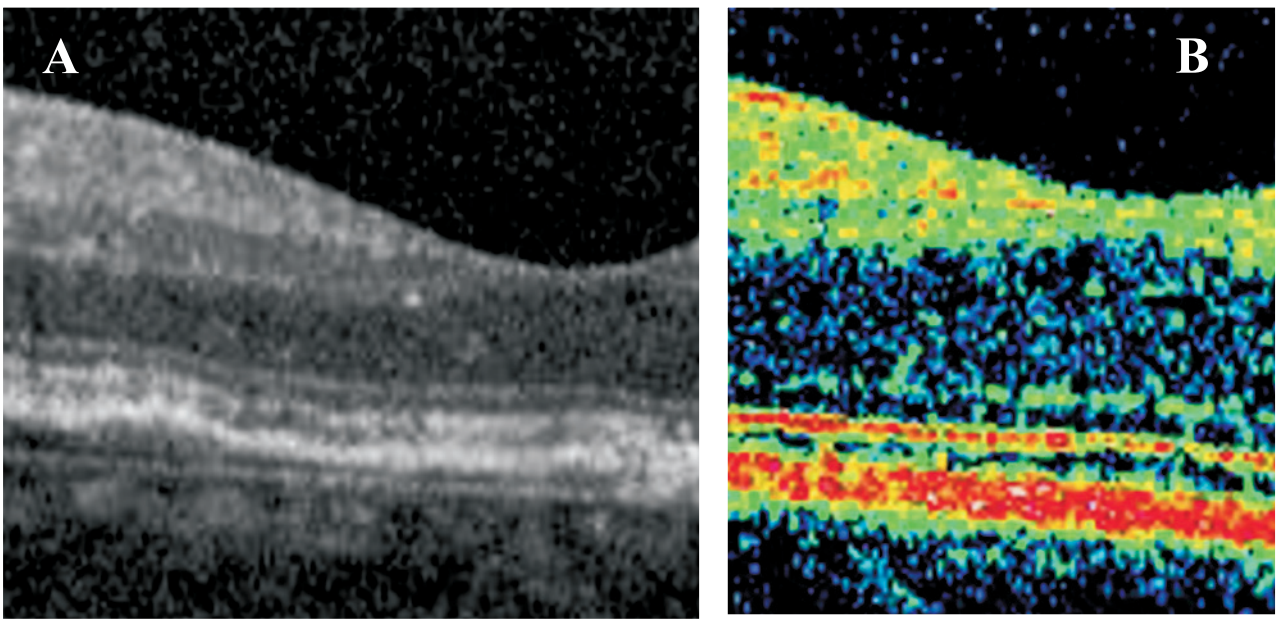


Figure 4: SD-OCT section (same case as in Figure 2).

A): The enlarged image clearly reveals 4 hyper-reflective lines (Bruch's membrane, RPE, IS/OS interface, external limiting membrane), and the hypo-reflective bands that separate these structures, particularly the outer and inner segments and limited PED.

B): The reference cross-section in a normal patient (false-color) reveals the IS/OS interface and the external limiting membrane but with lower resolution. Note the increased thickness of the outer segments in the center of the fovea.

Main Abnormalities of the RPE Band

Variations of RPE thickness are usually relatively mild and difficult to measure precisely because the limits of the RPE are poorly-demarcated, at least on Time-Domain OCT.

However, these variations can be assessed by observing more or less localized enhancement or attenuation of reflectivity.

Evaluation of these changes is more difficult on Time-Domain OCT due to the presence of relatively frequent undulations, which are artifacts due to eye movements.

RPE analysis is more precise with Spectral-Domain OCT, although changes related to the presence of drusen must be taken into account (**Figures 5 and 6**).

RPE Band Thickening

RPE band thickening could possibly be due to proliferation of the RPE, as observed on histological sections. RPE proliferations are barely perceptible on Time-Domain OCT.

Certain features on Spectral-Domain OCT are suggestive of localized proliferation of the RPE and are fairly frequently associated with occult choroidal neovascularization underneath the RPE, which itself may not be directly visible on OCT (**Figures 7 and 8**).

However, OCT correlation with pathology specimens of normal and AMD affected eyes are not available at the present time.

Marked thinning of the RPE can be observed, particularly in case of **RPE atrophy**.

The band corresponding to the RPE appears to be markedly thinned, usually linear, associated with hyper-reflectivity extending posteriorly into the zone of atrophy and enhancing this area.

Thinning of the entire neurosensory retina may also be observed over an RPE atrophy area, especially when it is extensive.

Spectral-Domain OCT can confirm this thinning, essentially corresponding to **alterations of outer layers**, as the external limiting membrane and IS/OS interface are interrupted and absent over atrophic RPE (**Figure 9**).

In more severe atrophy, the outer nuclear layer is altered or no longer detectable and the RPE appears to be in direct contact with the outer plexiform layer (**Figure 10**).

In extreme cases, such as after an RPE tear, the choroid (more or less atrophic) and the residual Bruch's membrane are exposed by the rolled up retracted RPE and are in contact with the inner layers of the retina (**Figure 11**).

Interruptions of the RPE

In some cases, discontinuity of the RPE is due to effraction or break of the RPE, which allows subretinal or intraretinal protrusion of choroidal structures.

The most typical example is that of chorioretinal anastomoses between choroidal neovascularization and juxtafoveal retinal vessels.

This type of lesion is rarely well-visualized on Time-Domain OCT but is better demonstrated on Spectral-Domain OCT.

The appearance of a chorioretinal anastomoses is even more marked with simultaneous angiography, which provides point by point overlay (**Figure 12**).

The **features of attenuated** RPE are usually due to shadowing or accentuated masking.

Masking is related to the presence of highly reflective structures (eg, pigment, hard exudates, and CNV) in the inner retinal layers. Masking is partial and progressive and corresponds to the density of overlying structures.

Masking may be due to retinal hemorrhage or accumulation of melanin pigment or lipofuscin.

Shadowing due to a hyper-reflective structure, such as the presence of classic CNV, must be recognized for early treatment (**Figure 1**).

IRREGULARITIES OF THE RPE

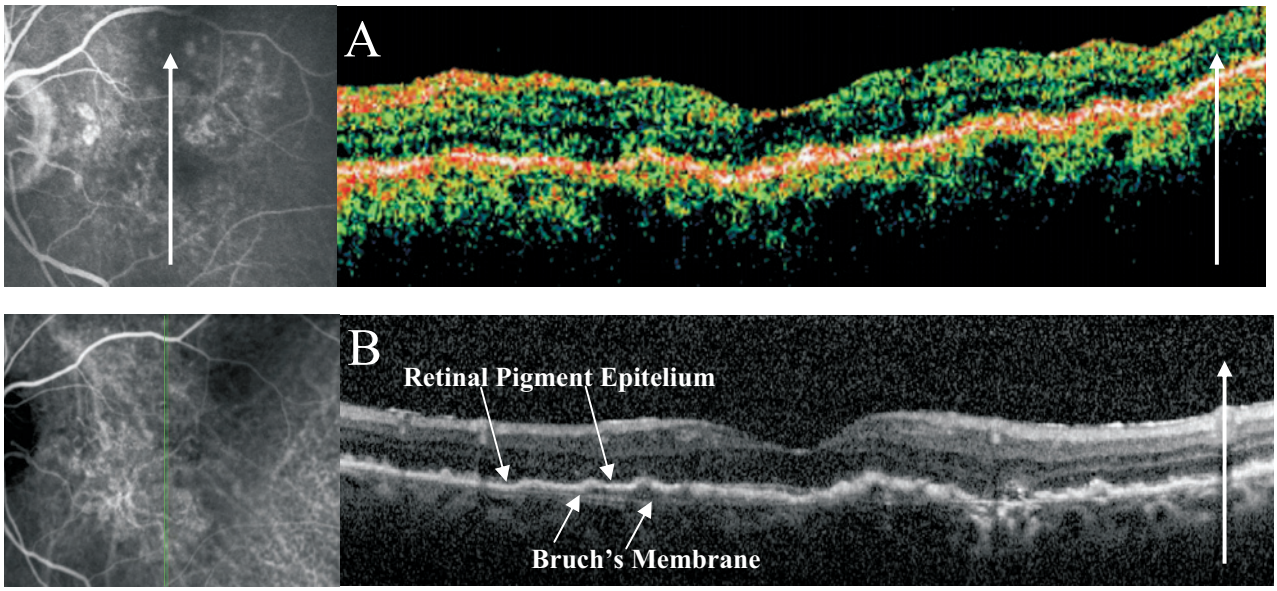
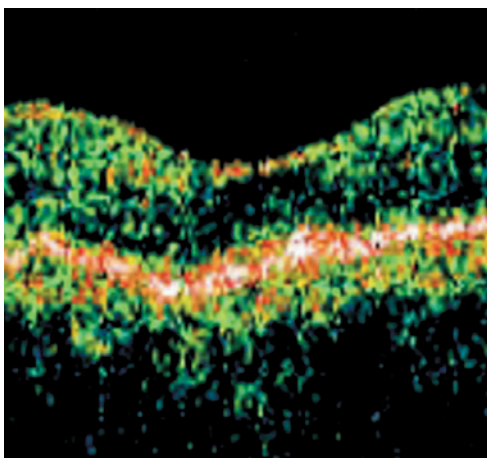


Figure 5: Thickness variations and irregularities of the RPE.

A): *Stratus vertical section shown with fluorescein angiography** (*abnormal choroidal network*):
Undulations from motion artifact limit the visibility of retinal structures.

B): *Spectralis vertical section correlated with ICG angiography** (*same patient*):
Multiple, more or less marked thickness irregularities over the entire length of the section.
Note the presence of several drusen and ability to visualize Bruch's membrane (short arrows), indicating an early PED.



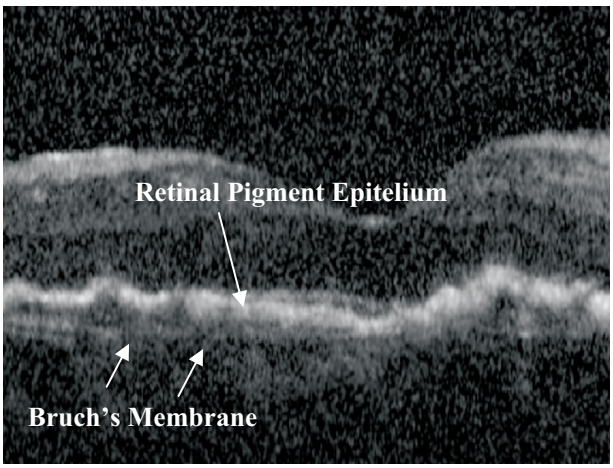
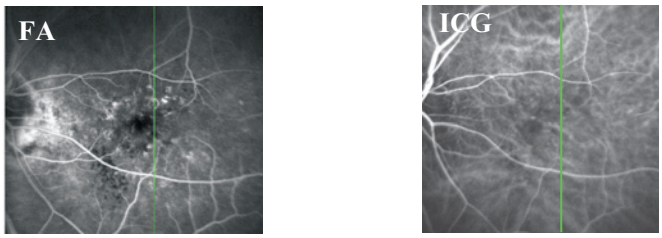
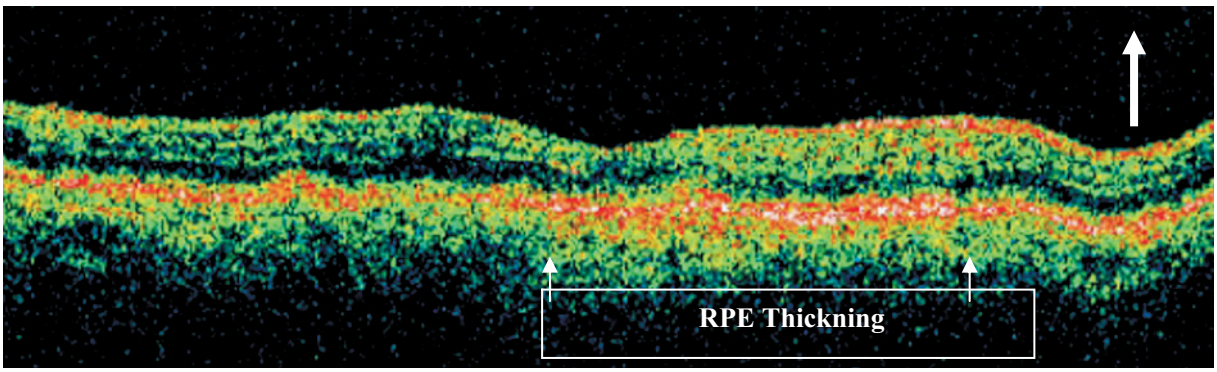


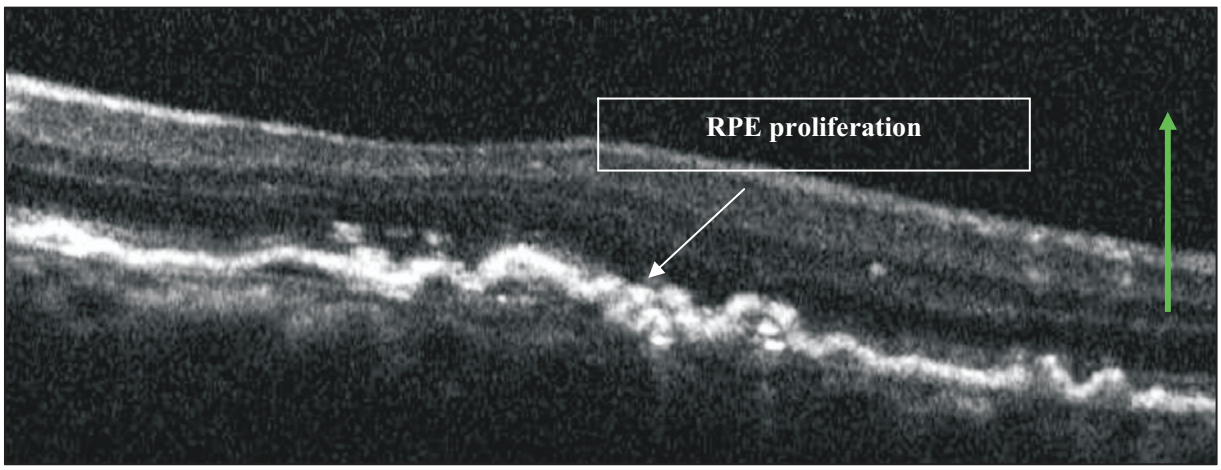
Figure 6: Thickness variations and irregularities of the RPE (same case as in Figure 7).

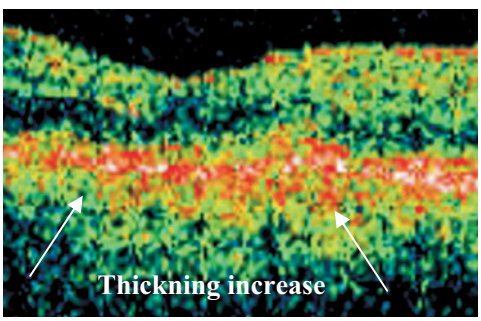
These enlarged views facilitate analysis of minimal changes in the thickness and reflectivity of the RPE and various alterations in adjacent layers.

RPE THICKENING AND PROLIFERATION









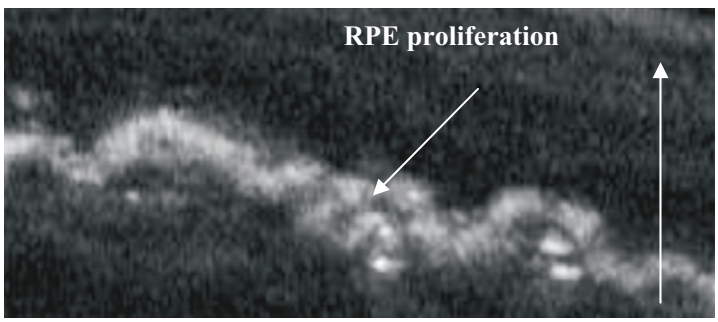


Figure 7: Increased thickness and proliferation of the RPE with limited detachment of the RPE.
A): *Stratus vertical section shown with fluorescein angiography** (*early occult CNV*): increased thickness only (arrows).
B): *Spectralis vertical section correlated with ICG angiography** (*same patient*): fairly marked irregularities of thickness with proliferation of the RPE (arrow) in the area of the CNV.
C): Increased thickness and proliferation of the RPE: Magnified view.

RPE PROLIFERATION

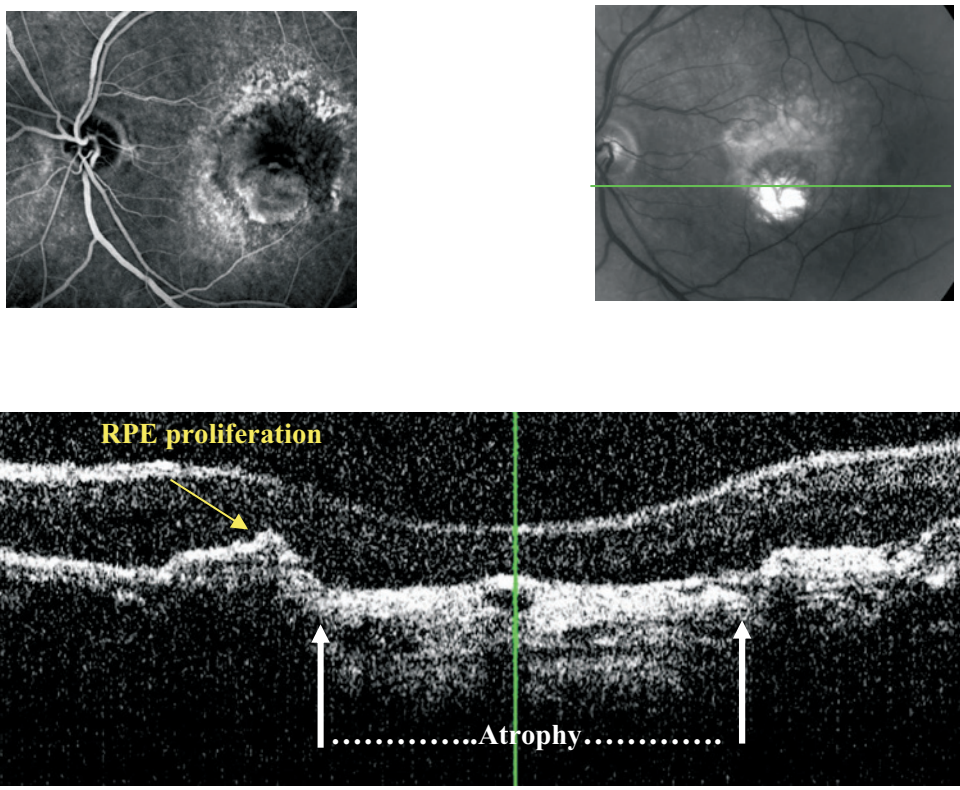


Figure 8: Proliferation of the RPE (adjacent to an area of laser-induced atrophy):

Spectralis* **section correlated with fluorescein angiography:**
Presence of a prominence on the RPE band, due to hypertrophy and underlying fibrosis, adjacent to the inferior para central laser scar (clearly visible with thinning of the retina, atrophy of the RPE, and hyper-reflectivity extending well posteriorly).

RPE THINNING AND ATROPHY

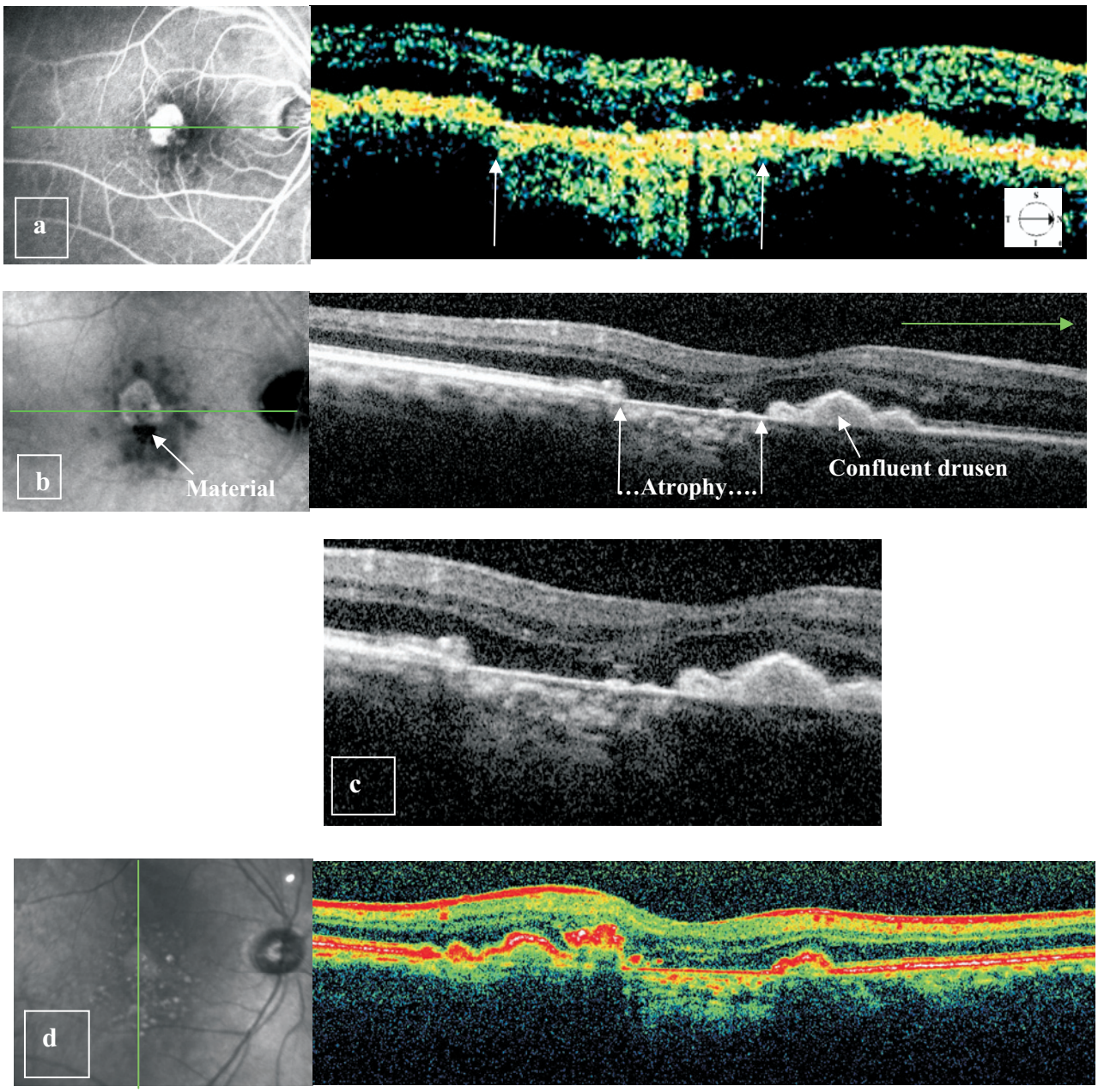


Figure 9: Area of RPE atrophy related to spontaneous resorption of deposits and associated with confluent soft drusen:

a): *Stratus horizontal section shown with fluorescein angiography** (*hyper-fluorescence related to atrophic resorption of deposits*).
On OCT, the area of RPE atrophy is seen as thinning of the RPE and posterior hyper-reflectivity.

b): *Spectralis horizontal section correlated with ICG angiography** (*black residual material; localized RPE atrophy [same patient]*).
On SD-OCT, the IS/OS interface and external limiting membrane are no longer visible in this atrophic zone.
Note the prominent confluent soft drusen on either side of the atrophic zone.

c): *Spectralis horizontal section**: enlargement of image (**b**).

d): *Spectralis vertical section correlated with an autofluorescence image** (*the residual material is autofluorescent*).
On SD-OCT, the false-color image also clearly demonstrates the localized atrophy of the RPE and the outer layers of the retina.

RPE THINNING AND ATROPHY AND LOSS OF PHOTORECEPTORS

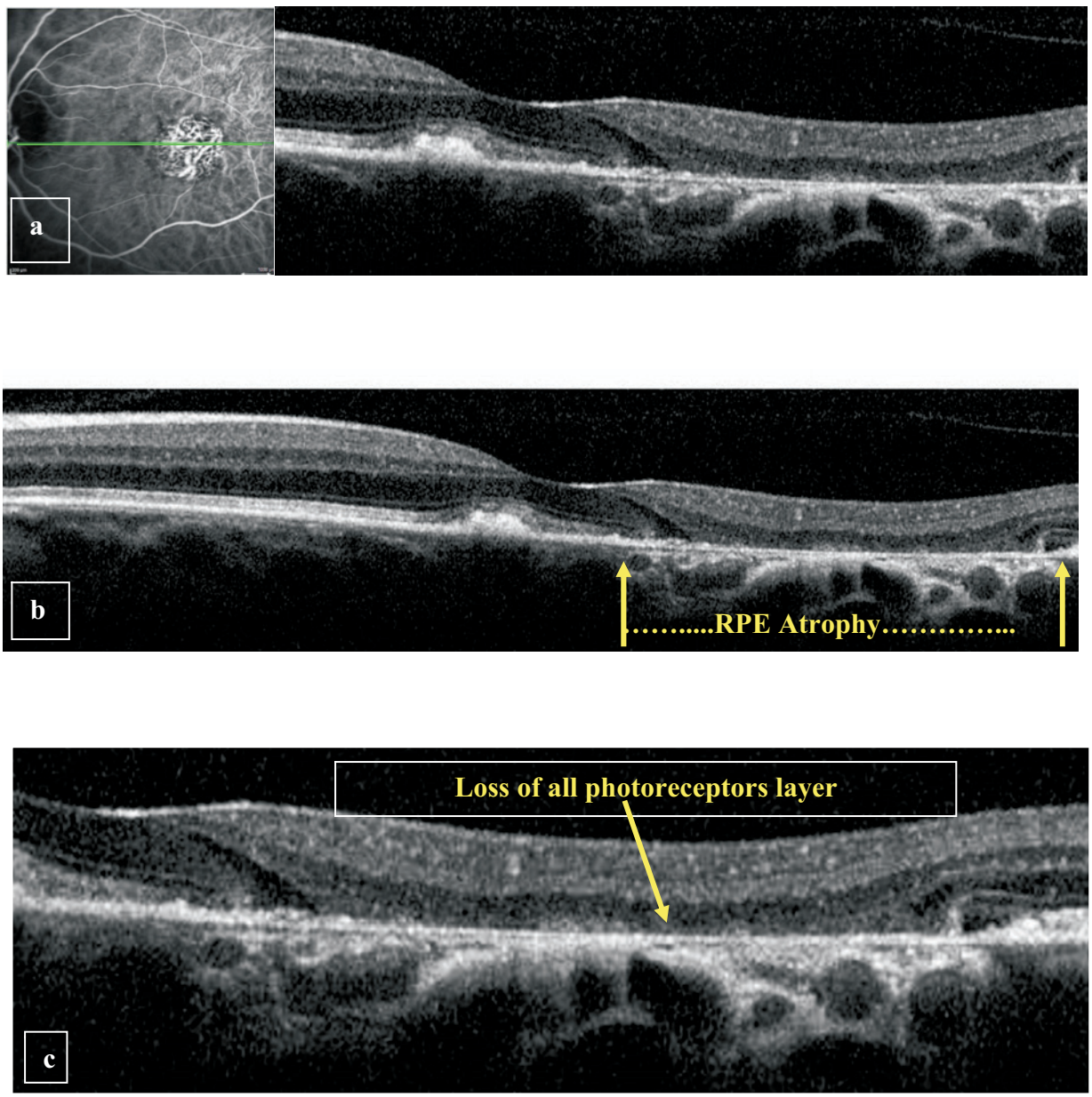


Figure 10: Area of thinning and RPE atrophy (related to resorption of deposits).

a): ICG angiography: *only a few large choroidal vessels are visible in the atrophic RPE area and choriocapillaris.*

b): *Spectralis horizontal section correlated with ICG angiography:** the localized RPE atrophy (yellow arrows) is associated with loss of the IS/OS interface, external limiting membrane, and even the outer nuclear layer, which is the result of the photoreceptor layer loss.

c): Enlarged view: Only the inner plexiform layer and retinal layers are still visible.

LOCALIZED LOSS OF THE RPE

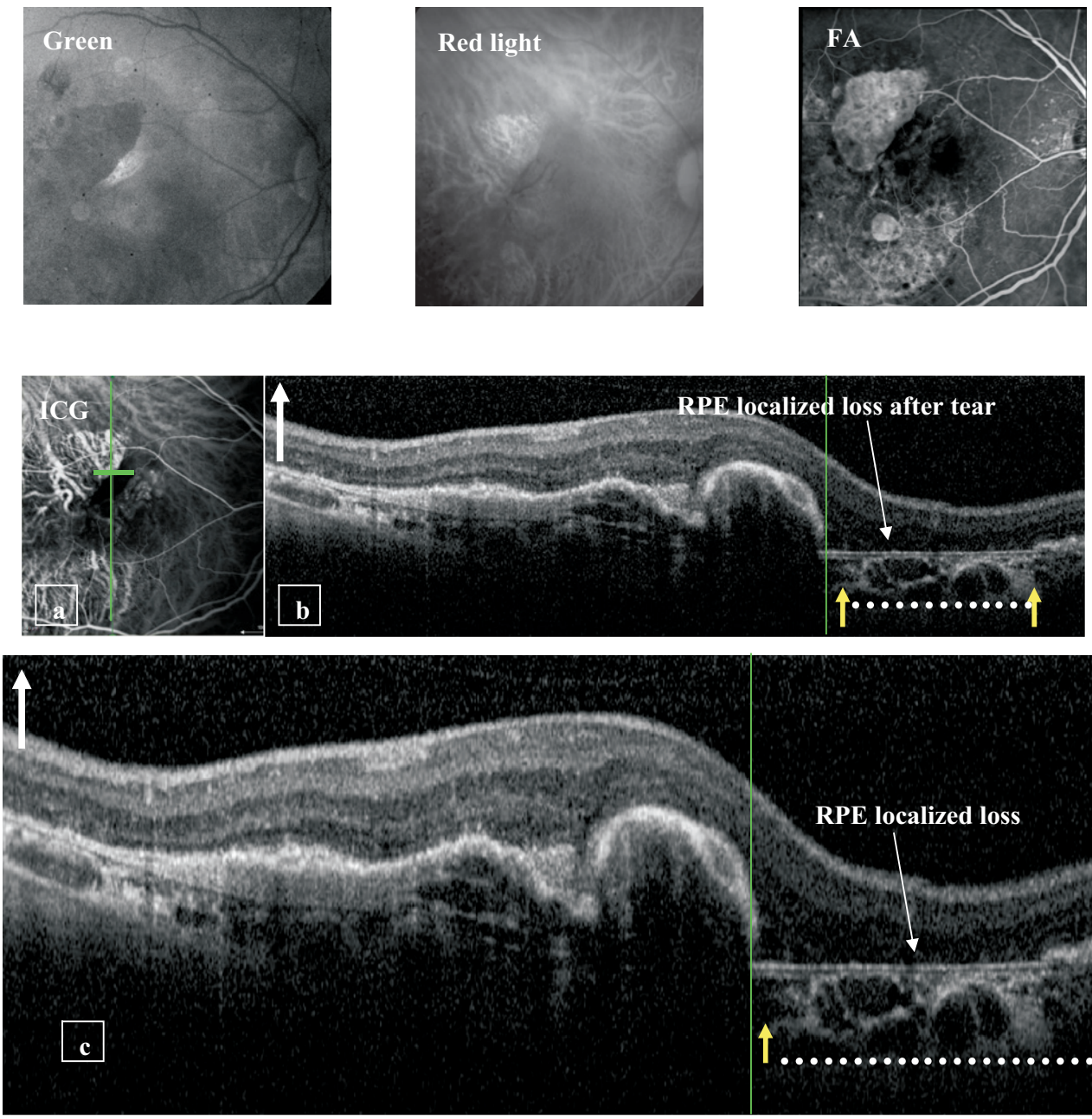


Figure 11: Localized absence of the RPE due to retraction after a tear.

a): ICG angiography: *in the superior region, a choroidal area is exposed by by the rolled-up retracted RPE that appears very dark and hypofluorescent. The inferior part corresponds to the residual PED.*

b): *Spectralis vertical section correlated with ICG angiography**: the residual PED is clearly visible, delineated by the retracted RPE. The RPE is no longer visible in the exposed zone. The atrophic choroid and Bruch's membrane are in contact with the inner retinal layers. The green line and calliper are located at the edge of the tear.

c): Enlarged view.

LOCALIZED DISRUPTION OF THE RPE

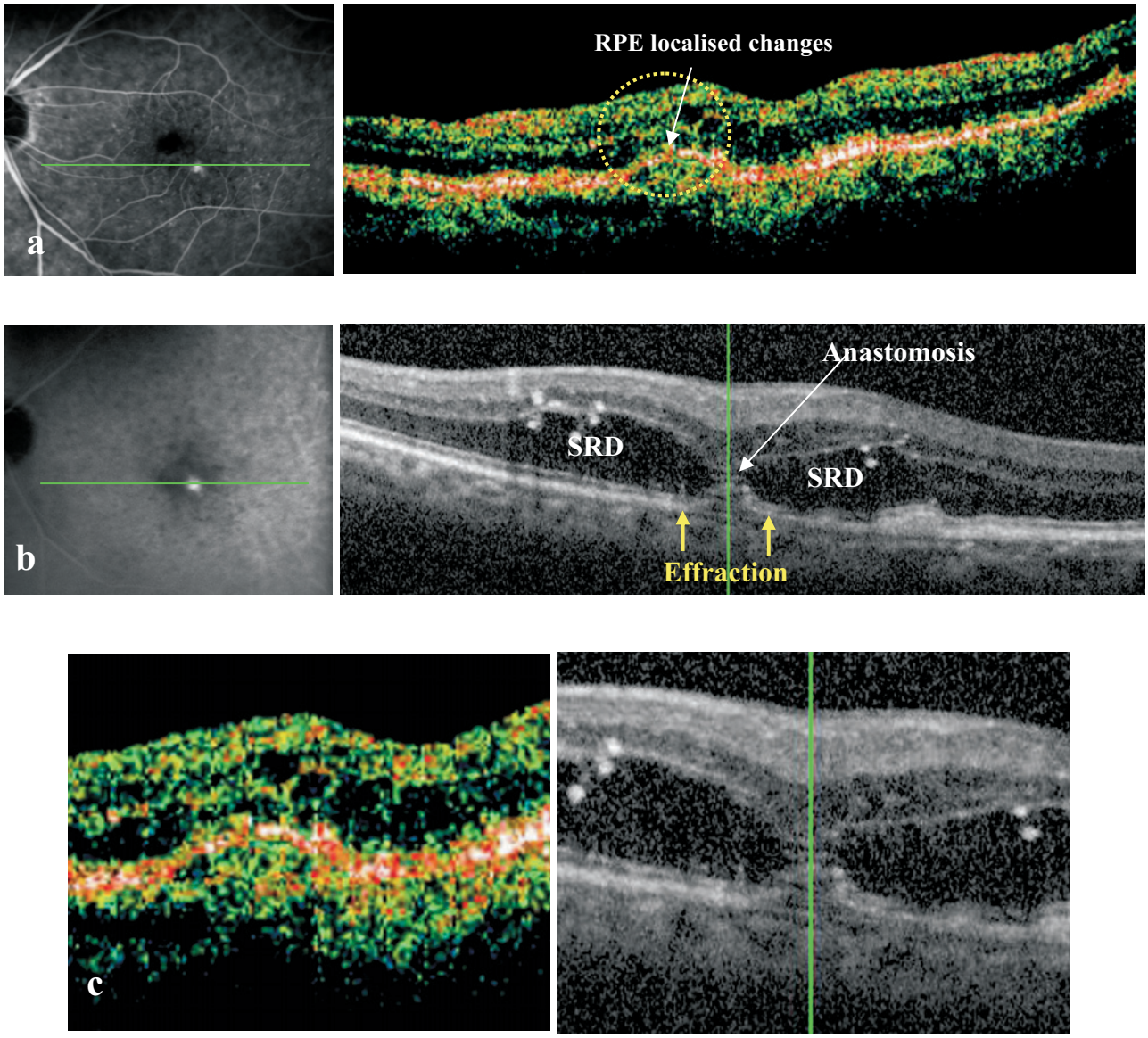


Figure 12: Break of the RPE (chorioretinal anastomosis).

a): *Stratus horizontal section shown with fluorescein angiography** (*juxtafoveal hot-spot*): the RPE band presents an isolated, limited, and localized abnormality: this juxtafoveal irregularity is accompanied by a small PED.

b): *Spectralis horizontal section correlated with ICG angiography (*same patient*)**: the RPE band is clearly visible almost throughout this image, accompanied by the parallel line of the the IS/OS interface. These two lines are suddenly interrupted over a limited juxta-foveal zone.
This break or effraction of the RPE exposes a moderately reflective structure, which appears to penetrate into the neurosensory retina, suggesting the presence of a chorioretinal anastomosis. It is demonstrated on angiographies and confirmed by other associated signs (small PED, accentuated exudation, SRF, intraretinal cysts).

c): Enlargement of previous images.
This zone of RPE rupture is not simply due to back-shadowing and should be clearly identified.

II. Posterior to the RPE Band

Many changes or signs located posterior to the RPE band are observed in the course of AMD.

Analysis of these signs provides a wealth of information. These changes are observed on both sides of **Bruch's membrane** (BM).

Bruch's membrane is adherent to the RPE and is not visible in normal eyes.

Visualization of the BM as a *distinct entity from the RPE* indicates localized loss of adhesion and ***detachment of the RPE***. This detachment may be minimal, moderate, or extensive.

The following signs may be observed between BM and RPE:

- *Accumulation of material* of variable density (drusen, deposits, fibrovascular tissue), or
- A*ccumulation of fluid*.

This fluid may be:

- Either **serous** and optically empty, or
- **Fibrinous** and moderately reflective, or
- **Hemorrhagic** and blocking light.

1. Accumulation of Material Posterior to the RPE: Drusen

Drusen

Drusen, frequently present in AMD, cause **elevation of the RPE**.

Drusen can be detected as soon as they are larger than the classical definition of soft drusen (greater than 63 µm). They may be isolated or multiple.

They induce very little loss of visual acuity when they are small but can have a more dramatic impact when larger.

TD-OCT

Drusen are *not optically empty*, but their cross-section appears to be **moderately hyper-reflective**, which distinguishes them from serous detachments.

This is a particularly important characteristic sign.

This moderate hyper-reflectivity (false green color with the *Stratus**) nevertheless allows visualization of the regular line of Bruch's membrane (**Figures 13 and 14**).

SD-OCT

Analysis of the IS/OS interface and **outer nuclear layer** over the drusen is very useful to assess their **effects**.

These structures remain clearly visible, continuous, and only slightly modified over *small or medium-sized drusen*.

However, **large confluent drusen** protrude into and alter adjacent retinal layers:

- The outer nuclear layer may appear thinned, sometimes with a jagged appearance.
- The external limiting membrane and IS/OS interface present localized disruptions over the apex of the drusen (**Figures 15-17**).

However, this disruption and alteration of these lines are sometimes more extensive, especially when adjacent to small areas of RPE atrophy (**Figure 18**).

Examination of these layers on sufficiently enlarged images provides direct signs of photoreceptor inner and outer segment damage, which may have a major prognostic value for follow-up of high-risk drusen.

ELEVATION OF THE RPE BY DRUSEN

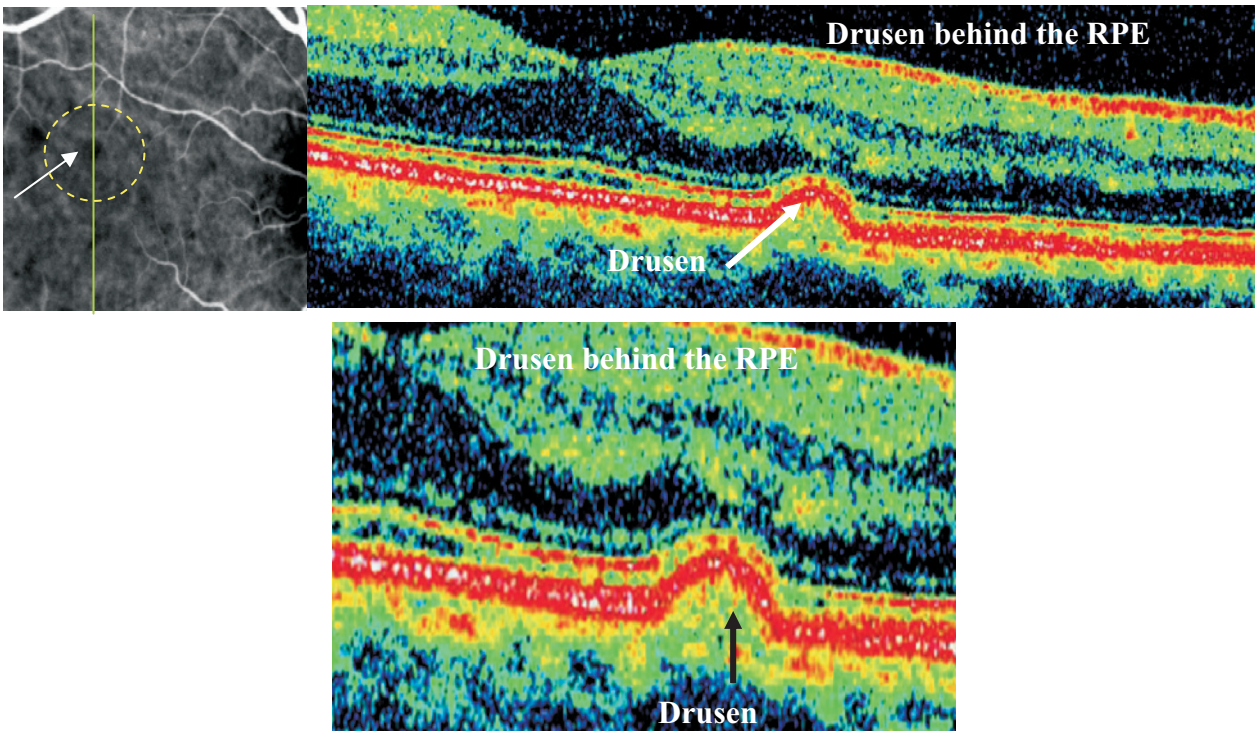


Figure 12: Localized elevation of the RPE related to the presence of a large soft drusen.
***Spectralis** vertical section combined with ICG angiography** (*persistent hypo-fluorescence of a large drusen*).
The drusen (arrow) induces moderately hyper-reflective elevation of the RPE without posterior shadowing. Bruch's membrane remains clearly visible. Note that the IS/OS interface and external limiting membrane are not disrupted but slightly altered with relative thinning of the outer nuclear layer.

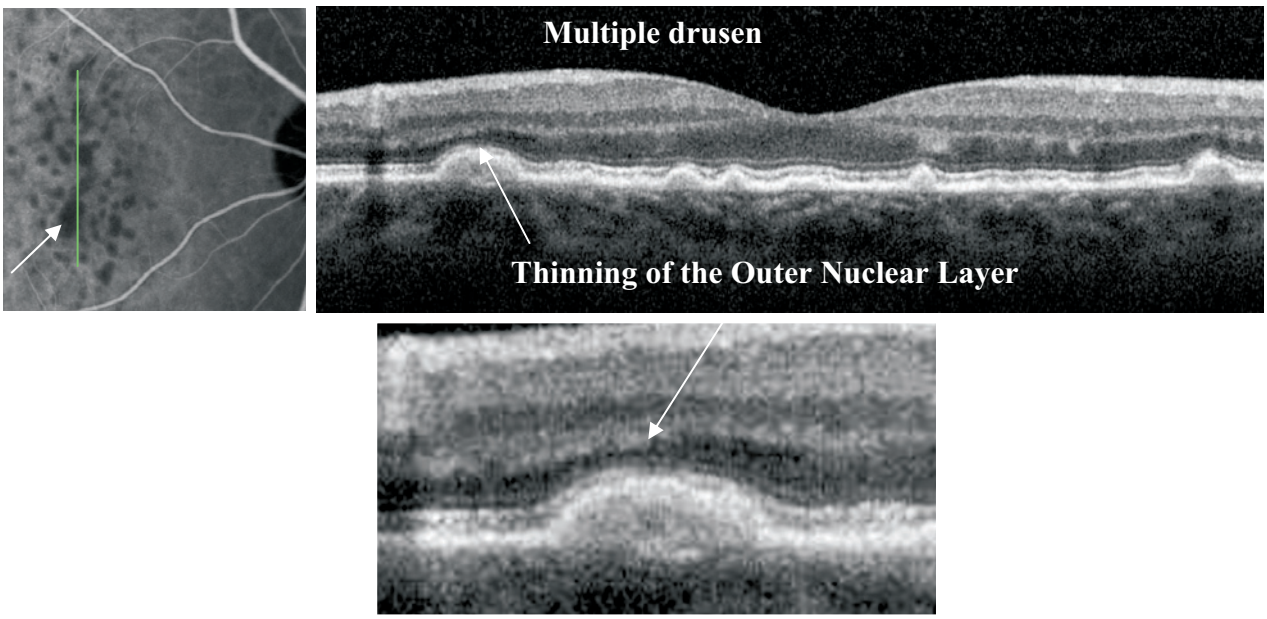


Figure 13: Multiple elevations of the RPE related to the presence of many soft drusen.
***Spectralis** vertical section combined with ICG angiography** (*persistent hypo-fluorescence of the drusen*).
The large drusen (enlarged view) induces marked elevation of the RPE, but the IS/OS interface and external limiting membrane are not disrupted and remain visible. However, the outer nuclear layer is considerably thinned.

MULTIPLE ELEVATIONS OF THE RPE BY DRUSEN

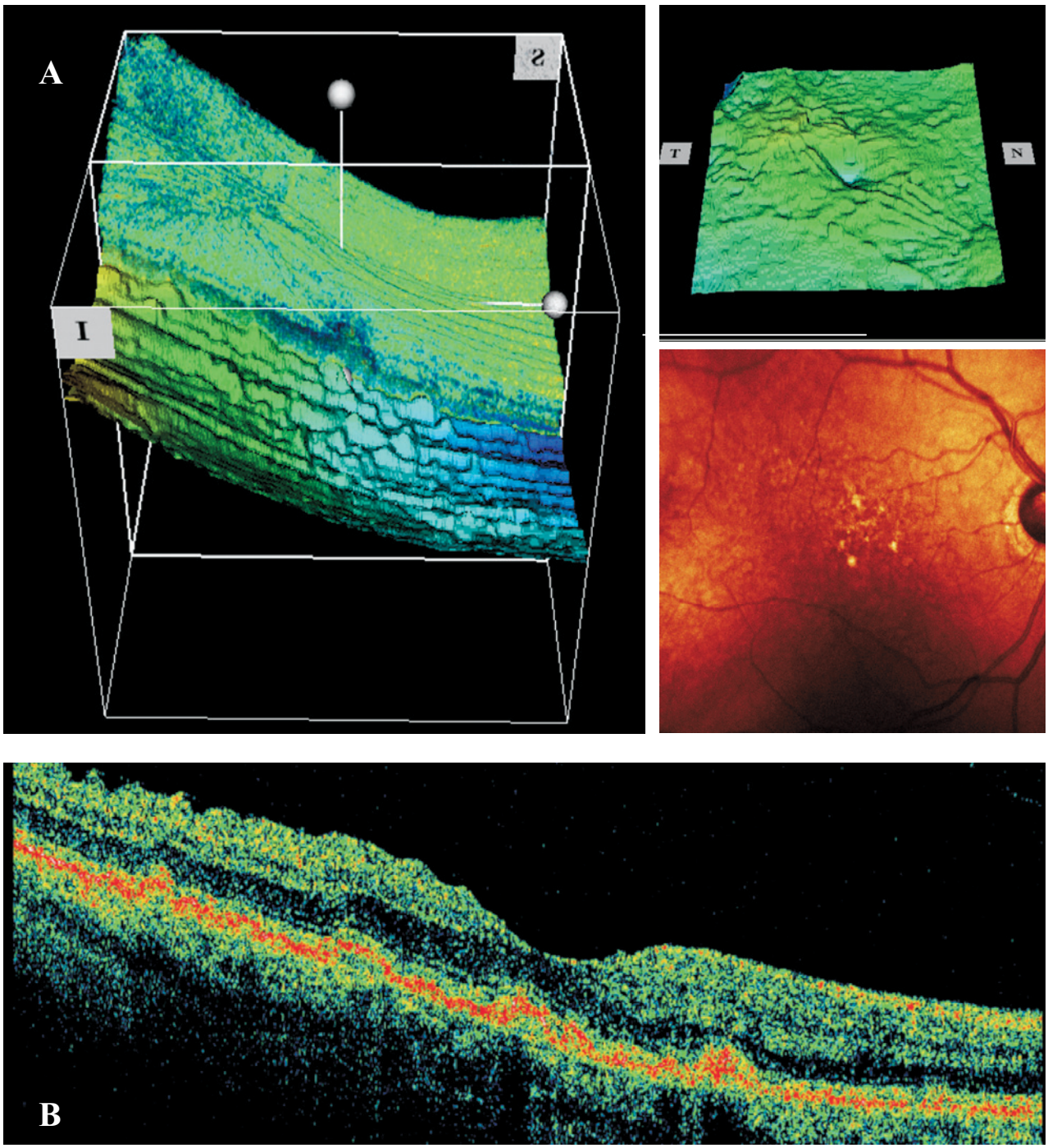


Figure 14: Multiple localized elevations of the RPE related to the presence of drusen.

***Topcon**: 3D image associated with surface images immediately posterior to the RPE.**

A): Section through the inferior part of the fovea, demonstrating multiple drusen immediately posterior to the RPE.

B): High-definition horizontal section demonstrating numerous drusen displacing the RPE.

MULTIPLE ELEVATIONS OF THE RPE BY DRUSEN

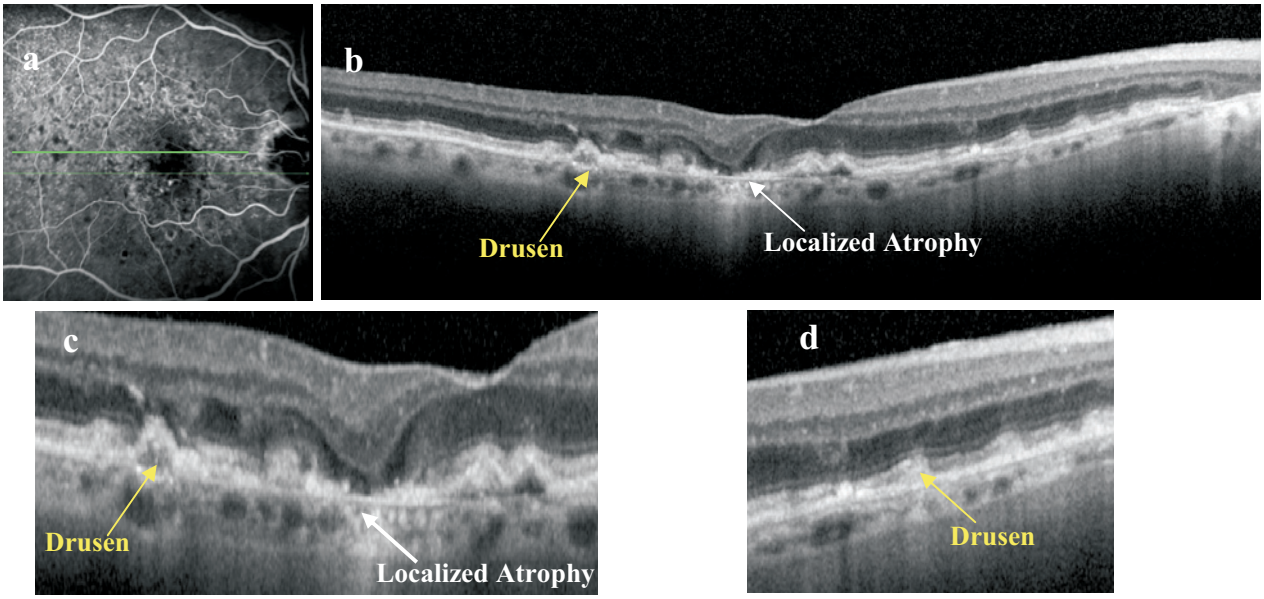


Figure 15: Multiple localized elevations of the RPE related to the presence of drusen.
a and b): *Spectralis horizontal section** *correlated with fluorescein angiography: slow staining of multiple drusen*.
On SD-OCT, drusen (*yellow arrow*) are moderately hyper-reflective with no posterior shadowing. Bruch's membrane is clearly visible.
c and d): Enlarged images: the prominent drusen modify and alter the continuity and thickness of the hypo-reflective outer nuclear layer, which appears thinned over the drusen. Note a small area of juxtafoveal atrophy (*white arrow*).
d): the external limiting membrane and IS/OS interface over the small drusen are not modified.

MULTIPLE ELEVATIONS OF THE RPE BY DRUSEN
Alterations of Retinal Outer Layers

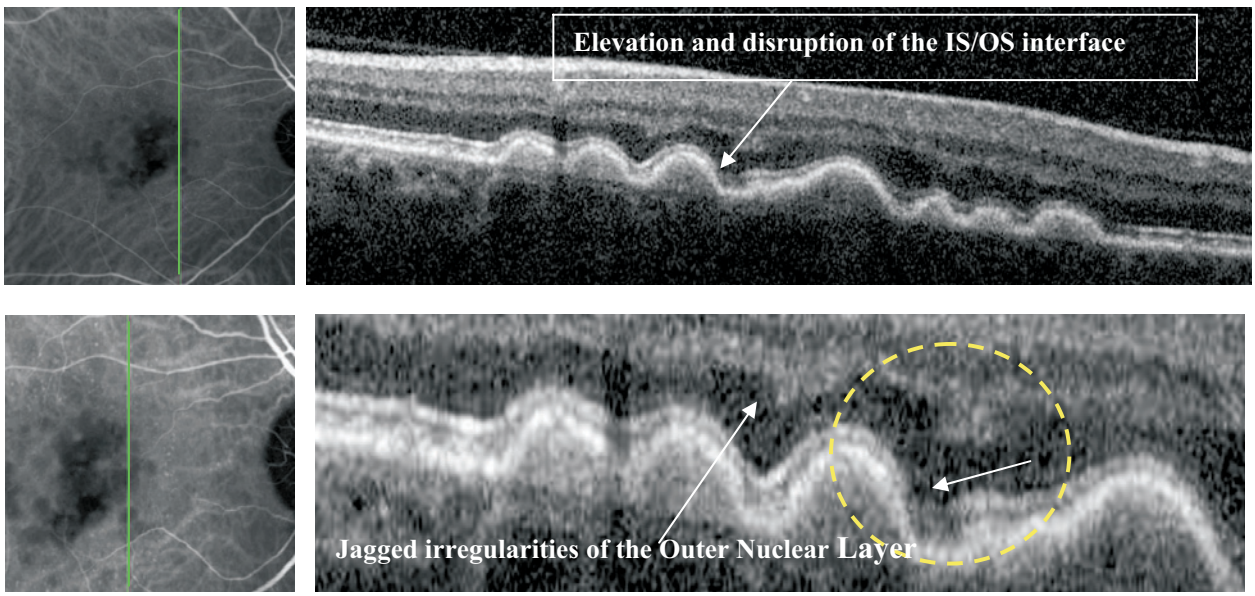


Figure 16: Multiple elevations of the RPE related to the presence of large soft drusen.
***Spectralis** vertical section correlated with ICG angiography** (*hypo-fluorescence of confluent drusen*).
The drusen have a homogeneous, slightly reflective content, which is well-delineated posteriorly by Bruch's membrane and causes moderate shadowing due to their volume.
The IS/OS interface and external limiting membrane remain visible, almost continuous, and only slightly modified with a localized disruption. The outer nuclear layer has several irregularities with a jagged appearance.

ELEVATION OF THE RPE BY LARGE DRUSEN

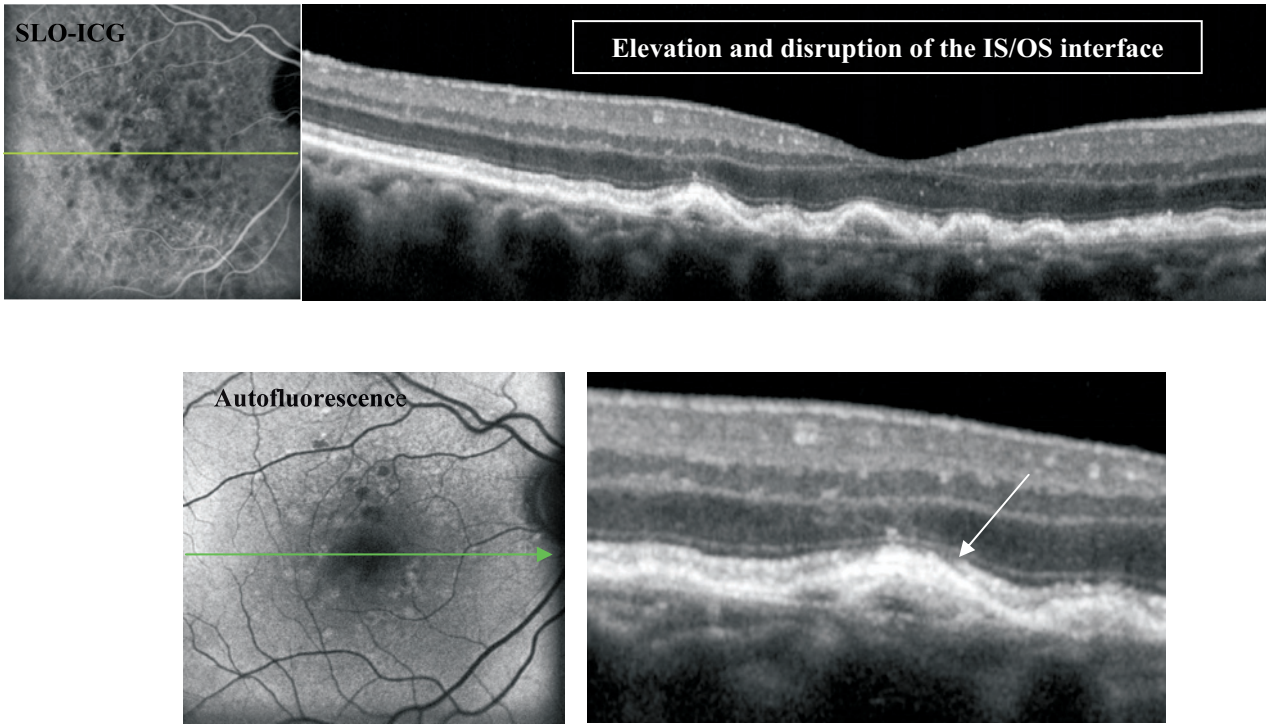


Figure 17: Elevation of the RPE, over a large soft drusen.

Spectralis* **horizontal section correlated with ICG angiography** (*hypo-fluorescence of drusen*).

Multiple drusen of various sizes are clearly delineated posterior to Bruch's membrane. The external limiting membrane remains clearly visible, but the IS/OS interface is disrupted at the apex of the drusen with slight alteration of the outer nuclear layer.
Note on the autofluorescence image, several dark areas of RPE atrophy over drusen.

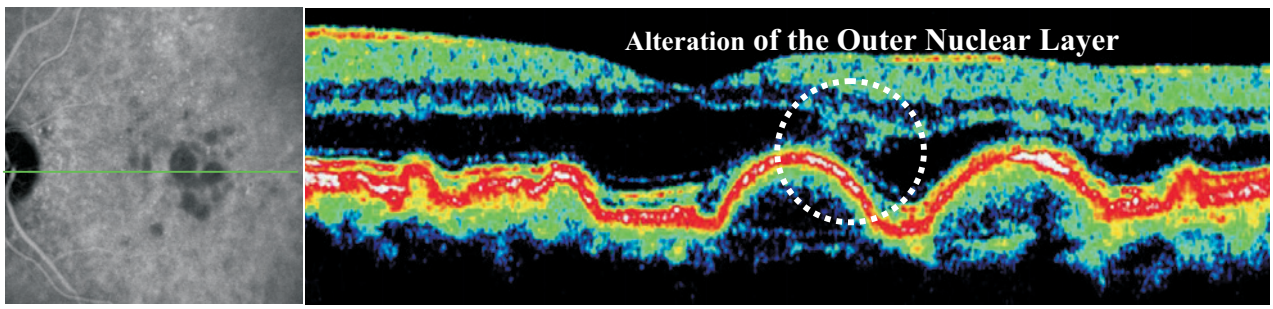


Figure 18: Multiple elevations of the RPE over very large drusen.

Spectralis* **horizontal section correlate*d* with ICG angiography** (*hypo-fluorescence of drusen*).

The cavity of the drusen presents a moderate but variable reflectivity. The BM is visible.
The outer nuclear layer is displaced and thinned over the apex of the drusen with increased density in some areas (*circle*).
The IS/OS interface is irregular and sometimes disrupted.

2. Accumulation of Material Posterior to the RPE: Drusenoid PED

Confluent soft drusen can cause more pronounced and more irregular elevation of the RPE.

Confluent drusen are sometimes sufficiently large to cause **drusenoid pigment epithelium detachments (PED)**.

A drusenoid PED, characterized by its irregular shape, is slowly but noticeably filled with dye and enhanced on *fluorescein angiography*.

Pigment migrations are often present in drusenoid PEDs, forming geometric or star shapes, and lipofuscin pigment accumulation may sometimes be observed.

On ICG angiography, drusenoid PED remains markedly hypo-fluorescent until the very late phase of the angiogram.

TD-OCT

The RPE remains regular and homogeneous but can also be thickened and have irregularities. Many drusen are visible adjacent to the RPE.

The cavity of a drusenoid PED is not optically empty but moderately hyper-reflective, similar to that of soft drusen, leaving the straight line of Bruch's membrane clearly visible. Partial or minor shadowing may be observed.

SD-OCT

Modifications of the IS/OS interface and external limiting membrane may be minor or moderate, with simple displacement of these structures by the drusenoid PED.

However, most cases present marked alterations at the apex of the PED, similar to those observed with large drusen.

Alterations of the IS/OS interface (thickened or undetectable), and disruptions of the external limiting membrane may be observed.

Alterations of the outer nuclear layer are even more important for prognosis. The outer nuclear layer may be thinned, more highly reflective, and irregular with a jagged appearance in drusenoid PEDs.

When the lesion is mainly central, all of this area may be displaced with loss of the foveal depression (**Figures 19 and 20**).

Patients presenting these alterations must be carefully examined to detect the presence of *intraretinal fluid,* suggestive of neovascular complications that should be identified as early as possible.

3. Accumulation of Material Posterior to the RPE

Posterior to the RPE (and sometimes also in contact with and/or anterior to the RPE), lipofuscin deposits can raise a number of problems.

Clinically, these deposits are **polymorphous** and vary in dimension, location, or in their association with extensive lesions. They may sometimes be reorganized as a result of complications.

On OCT sections, this **vitelliform** material may be situated anterior to or fused with the RPE, causing regular and moderate elevation of the RPE, but without an *exudative reaction*.

Accumulation of material induces posterior **masking** of the choroid (**Figure 21**).

These features are sometimes difficult to distinguish from choroidal neovascularization. The diagnosis is based on the presence or absence of associated exudative signs.

This material may be responsible for posterior hyperreflectivity, simulating fibrosis and sometimes optically empty zones, suggesting a neovascular process. This material can also spread and proliferate anterior to the RPE and even extend into the neurosenory retinal layers (**Figures 22-26**).

ELEVATION OF THE RPE BY DRUSENOID PED VOLUMINEUX

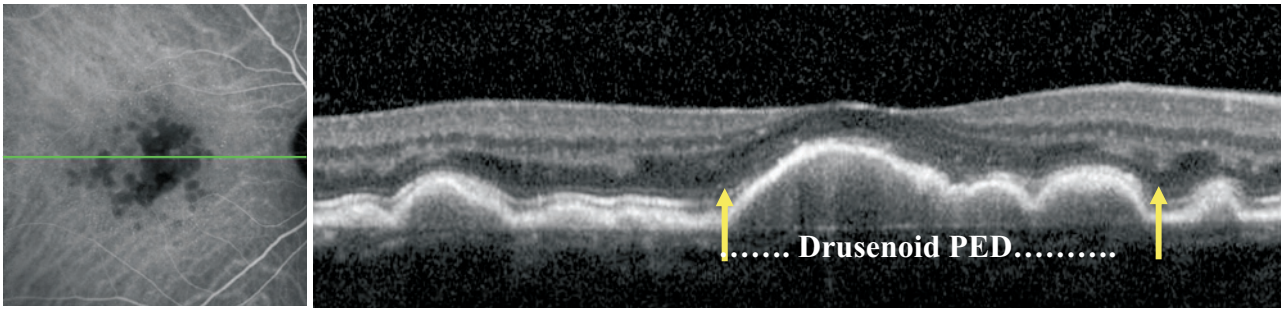


Figure 19: Elevation of the RPE–confluent soft drusen with a central drusenoid PED.

***Spectralis** horizontal section correlated with ICG angiography** (*drusen and drusenoid PED appear black*).

The **SD-OCT** section demonstrates several drusen of different sizes that have become confluent in the central zone measuring half a disc diameter. Retinal layers are displaced but their normal architecture is preserved.
However, the external limiting membrane and the IS/OS interface are relatively poorly-defined. There are no signs of abnormal fluid accumulation.

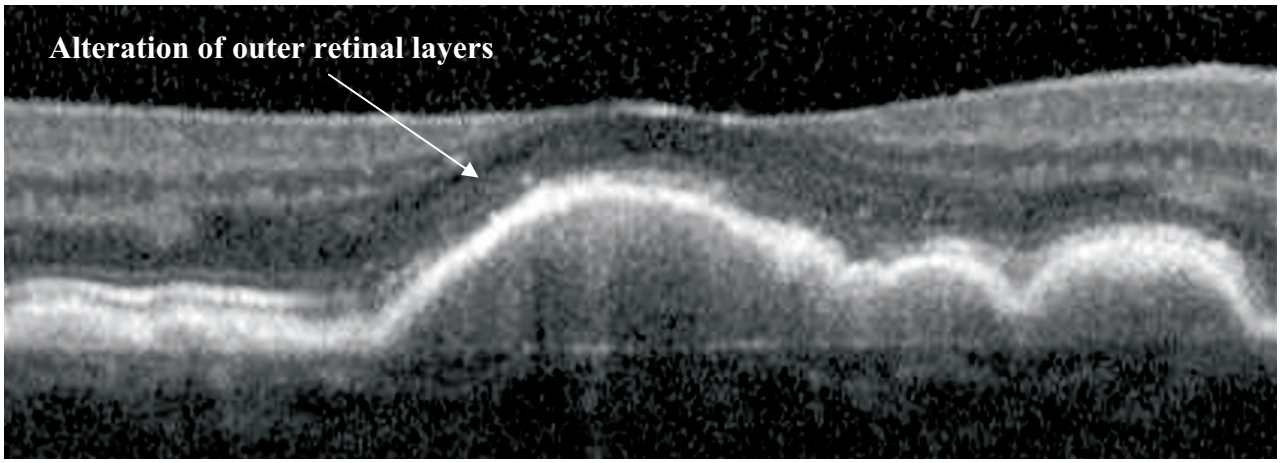


Figure 20: Elevation of the RPE–confluent soft drusen with a central drusenoid PED.

***Spectralis** horizontal section (enlargement of the previous image).**

The line of the IS/OS interface and the thinner line of the external limiting membrane are less clearly visible over the dome of the drusenoid PED.
The IS/OS interface appears to be replaced by a more dense signal, extending into the outer nuclear layer.
These features are suggestive of localized photoreceptor damage.

Note displacement of all of the retina and loss of the foveal depression. However, the normal architecture of all retinal layers appears to be not significantly altered.

ELEVATION OF THE RPE–ACCUMULATION OF VITELLIFORM MATERIAL

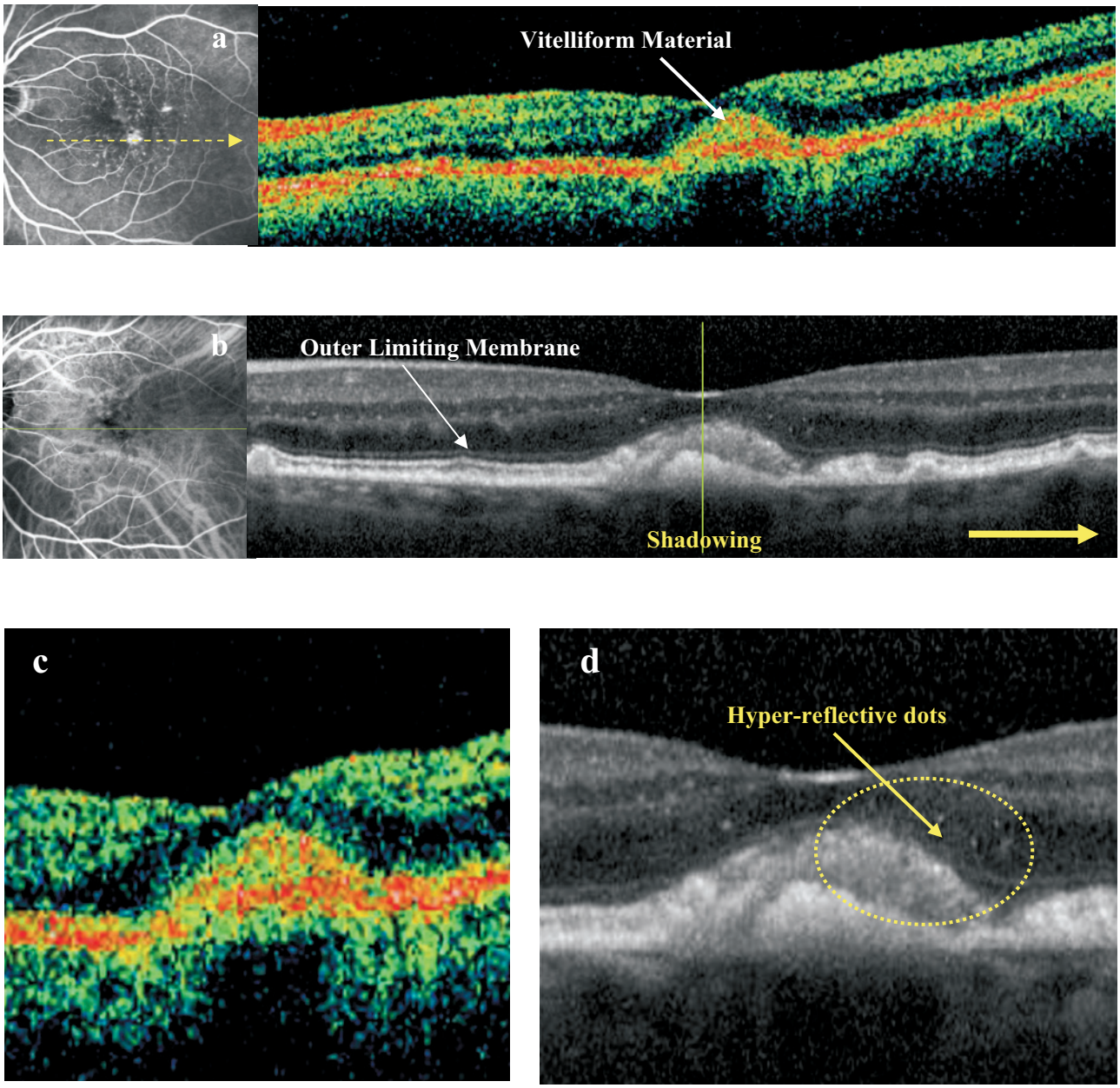


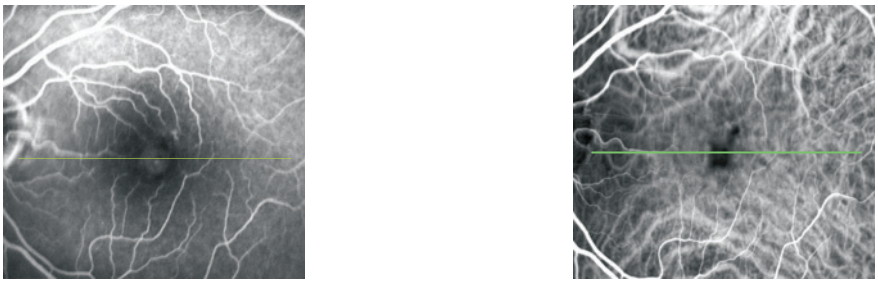
Figure 21: Elevation of the RPE–Accumulation of material posterior and anterior to the RPE (VA: 20/50).

a): *Stratus horizontal section correlated with fluorescein angiography** *(late staining of the material).*
On **TD-OCT**, this material seems to bulge or thicken the RPE with a pronounced posterior shadowing.
This lesion could also be suggestive of classic CNV, but there is no fluid or fluorescein leakage.

b): *Spectralis horizontal section combined with ICG angiography** *(material still hypo-fluorescent on late phase*).
On **SD-OCT**, the material forms a heterogeneous, protruding area, which merges with the RPE and displaces the IS/OS interface making it less clearly visible. The external limiting membrane remains clearly visible. Note the presence of intraretinal hyper-reflective bright spots.

c and d): enlargements of **(a)** and **(b).**

ELEVATION OF THE RPE - ACCUMULATION OF VITELLIFORM MATERIAL



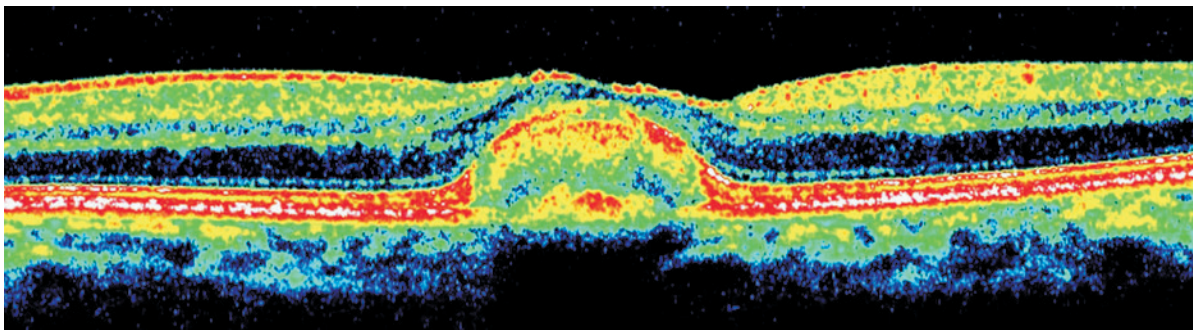


Figure 22: Elevation of the RPE–Accumulation of material posterior to the RPE, suggesting pseudo-vitelliform dystrophy (VA: 20/40).
***Spectralis** horizontal section combined with fluorescein angiography** (*progressive hyper-fluorescence, while ICG angiography shows persistent hypo-fluorescence).*
On OCT, the material is bulging or thickening the RPE with marked posterior shadowing. This lesion could also be suggestive of occult CNV, but ICG angiography and the absence of fluid exclude this diagnosis.

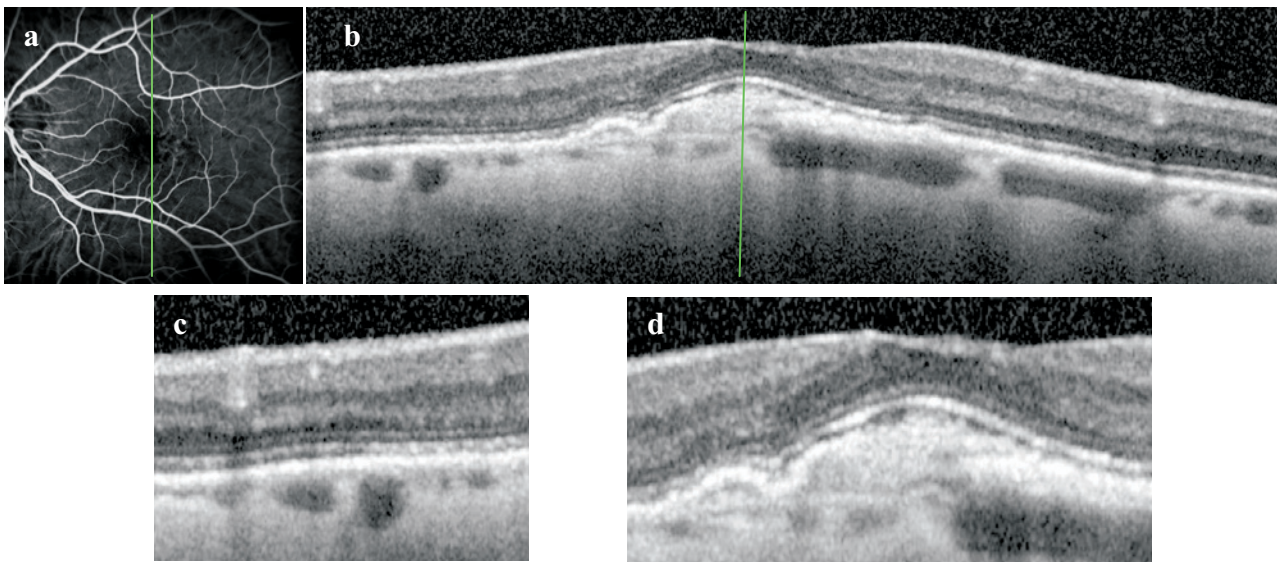


Figure 23: Elevation of the RPE–Accumulation of material posterior to the RPE (VA: 20/32).
a and b): *Spectralis vertical section combined with ICG angiography** (*partial late staining of the material*).
On OCT, the heterogeneous material lifts the RPE, displacing the IS/OS interface, which appears thicker and denser. Both the IS/OS interface and the external limiting membrane appear fragmented.
c and d): Enlarged images: compare the outer layers in the normal zone to the area of material accumulation, which shows marked irregularities and thinning of the outer nuclear layer. The foveolar zone is only slightly modified, accounting for the good visual acuity.

ELEVATION OF THE RPE–ACCUMULATION OF MATERIAL

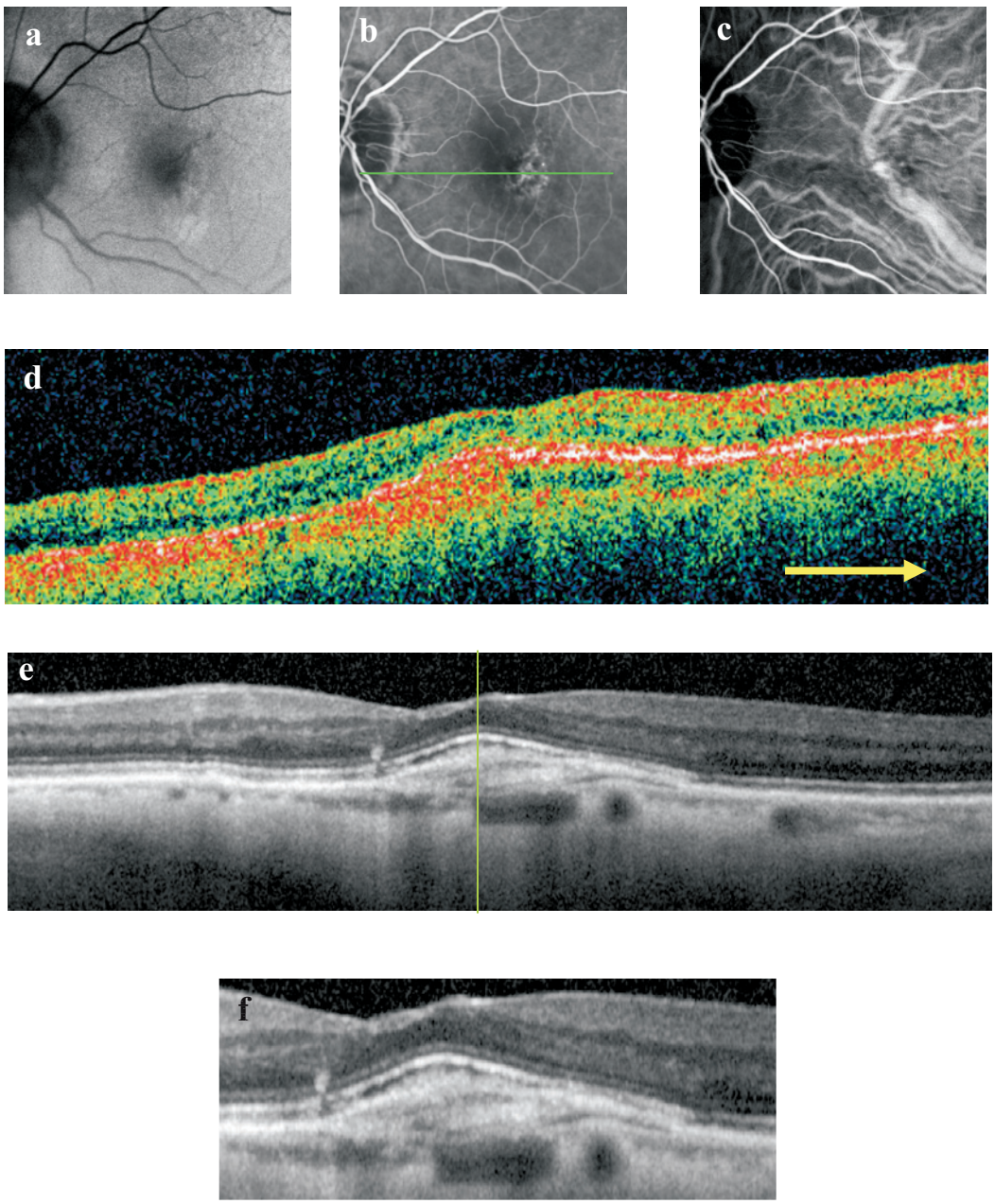


Figure 24: Elevation of the RPE–Accumulation of material posterior to the RPE (VA: 20/40).

a, b, and c): Autofluorescence, fluorescein angiography, and ICG angiography: *Juxtafoveal and subfoveal deposit of heterogeneous material with late hyper-fluorescence but without leakage.*

d): *Stratus horizontal section: On TD-OCT**, the material is heterogeneous, dense in the nasal part and, on the contrary, hypo-reflective in the temporal part, which could suggest an exudative reaction. However, the absence of fluorescein leakage argues against a neovascular complication.

e): *Spectralis horizontal section: On SD-OCT**, the material raises the band of RPE with a heterogeneous structure adherent to the RPE. The IS/OS interface (which remains clearly visible) is displaced with the external limiting membrane. Note the outer nuclear layer thinning.

f): Enlargement of image (e).

ELEVATION OF THE RPE–ACCUMULATION OF MATERIAL

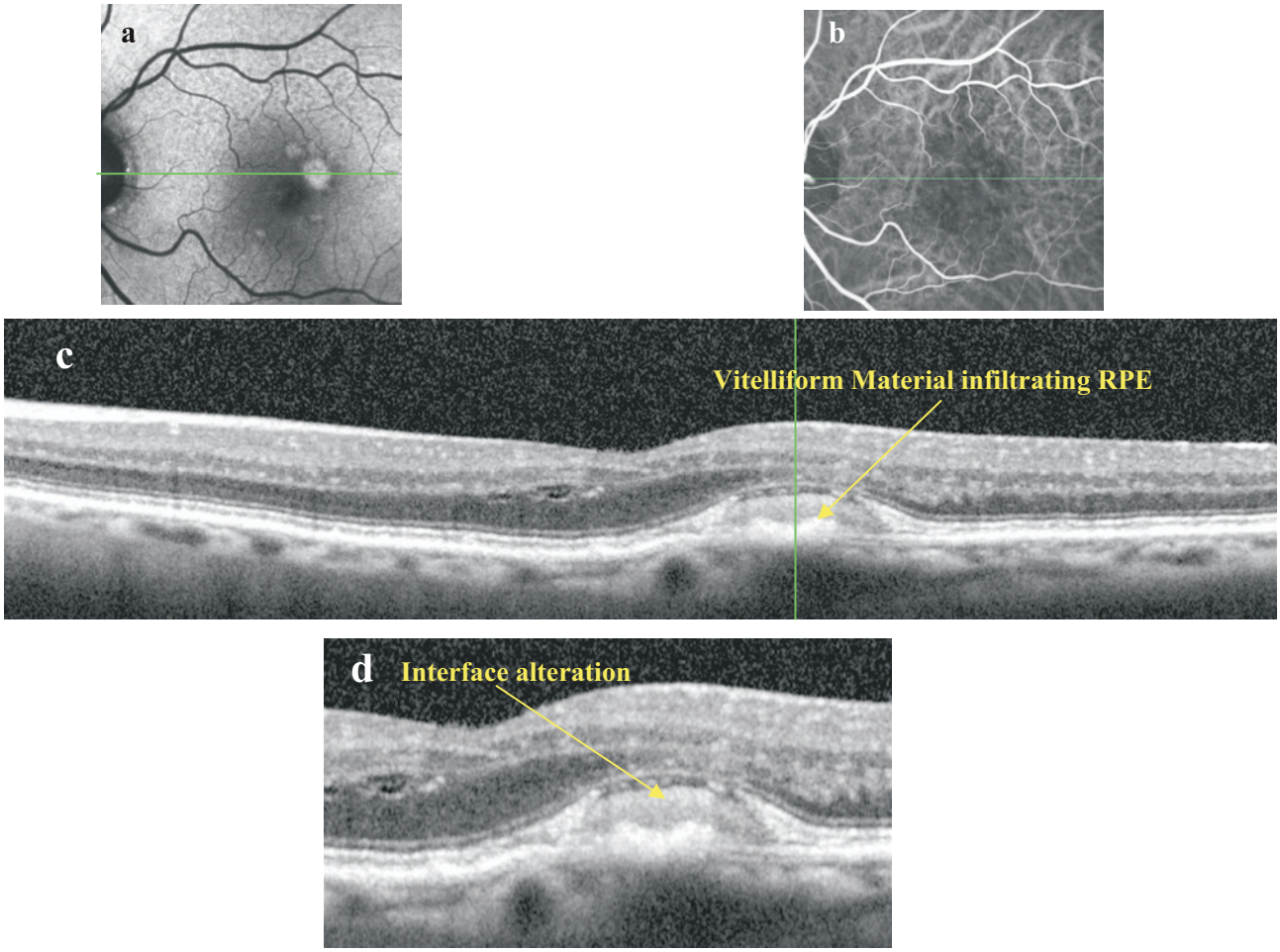


Figure 26: Elevation of the RPE–Accumulation of material posterior and anterior to the RPE.
a and b): Autofluorescence and ICG angiography: *presence of a dark temporo-foveal area of autofluorescent material with delayed ICG staining.*
c): *Spectralis vertical section.**
d): Enlarged image of (c): On SD-OCT thickening and hyper-reflectivity of the RPE in the center of the lesion induces relative masking. The material also accumulates anterior to the RPE, lifting and deforming the IS/OS interface and nuclear layer.

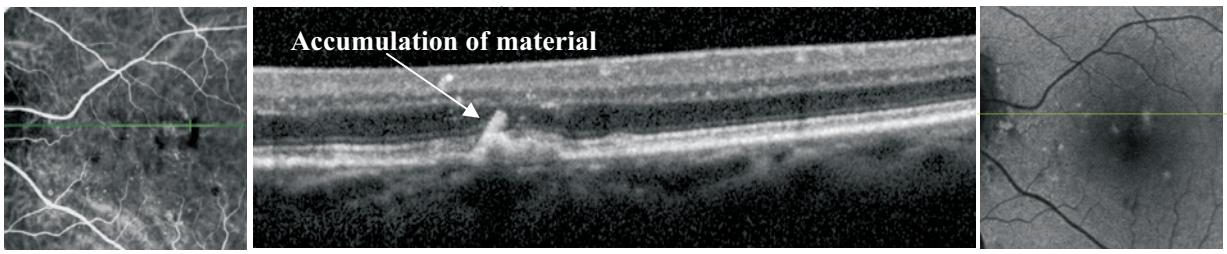


Figure 26: Elevation of the RPE–Accumulation of material posterior and anterior to the RPE (VA: 20/63).
***Spectralis** horizontal section combined with ICG angiography** *(hypo-fluorescent material)*. The material is hyper-fluorescent on the autofluorescence image.
On OCT, the material lifts the RPE, but also appears to extend within the retina.

4. Posterior to the RPE: Serous and Fibrovascular PED

Proliferation of choroidal neovascularization underneath the RPE (occult CNV) directly induces detachment of the RPE, which separates from BM.

The pigment epithelium detachment (PED), initially minimal then moderate, may, depending on the volume of exudation and the extent of the choroidal neovascularization (CNV), become very large.

a) Predominantly Serous PED

Accumulation of fluid in the space between the RPE and BM may be predominant or may even **appear to be isolated** depending on the location of the cross-section.

- *The PED* is then **essentially serous** and appears optically empty. The RPE band outlines the detachment. The elevation is regular, **dome-shaped**, of variable prominence and gently sloping (at least in the early stages) (**Figure 27**).

- *Choroidal occult neovascularization* is barely visible on OCT.

- During natural history or after treatment, the PED may take on a **multi-lobed** appearance with a wavy surface and variable size (**Figure 28**).

Successive OCT scans and the various **graphic representations** demonstrate either persistence, flattening, or scarring, as well as other retinal inflammatory response.

This sub-RPE exudative reaction appears to be much **less sensitive to treatment** than subretinal fluid accumulation or intraretinal infiltration.

The PED thickness should be frequently assessed in retinal thickness measurements after treatment to distinguish thickness related to leakage from that related to the presence of fibrous tissue.

b) Fibrovascular PED

- Exudation from CNV and fibrovascular tissues is less pronounced, and the PED cavity is **moderately hyper-reflective and heterogeneous**.

Only part of the cavity appears to be optically empty and filled by fluid.

Moderately reflective zones (false-green color on TD-OCT) are also observed.

The hyper-reflectivity is often limited to a **small band underneath the RPE**, but can fill almost the entire cavity (**Figure 29**).

- **Typical fibrovascular PEDs** are probably the most frequent form of ***occult sub-RPE choroidal neovascularization in AMD***.

Choroidal neovascularization in fibrovascular PEDs is rarely visible on OCT but usually seen on ICG angiography (**Figure 30**).

Various signs of progression on OCT (*hyper-reflective bright spots, dense zones, alterations of outer layers*) may be associated.

c) Two types of vascularized PED

- Predominantly bullous and serous or,
- Predominantly fibrovascular (slightly leaking).

These two forms can also coexist in varying degrees during the course of the disease.

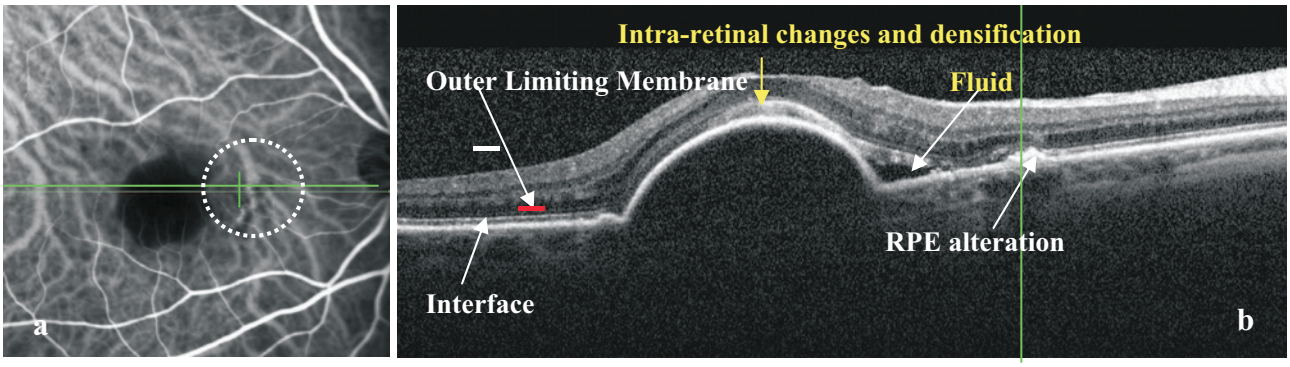
This is especially the case for chronic forms that gradually become *organized.* All these lesions induce little or no posterior shadowing and Bruch's membrane remains visible.

- During the course and usually in response to treatment, the PED detachment gradually collapses. The vascularized PED often becomes **multi-lobed with a wavy** appearance and an extensive but relatively flat profile.

At the same time, its cavity becomes organized and increasingly reflective, suggesting the development of fibrosis (**Figures 31-34**). This is confirmed by fluid resorption and progressive reattachment of the retina.

However, on SD-OCT, changes, organization, or even loss of the outer retinal layers persist or may be accentuated over the fibrosis and are associated with gradual and **irreversible functional impairment**.

POSTERIOR TO THE RPE: SEROUS PED



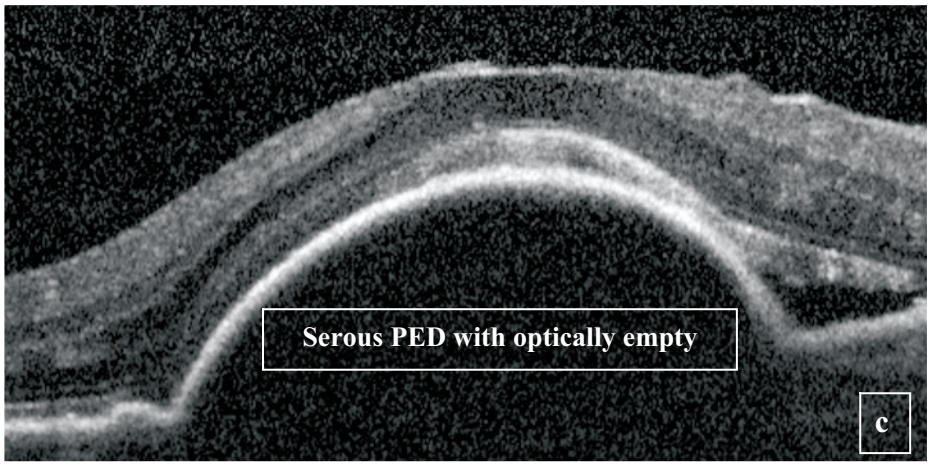


Figure 27: RPE detachment: Large serous detachment posterior to the RPE and occult CNV.

a): ICG angiography: *serous PED adjacent to occult CNV. The PED is rounded and markedly hypo-fluorescent. It is well-delineated with a nasal notch which corresponds to the CNV.*

b): Spectralis* horizontal section.

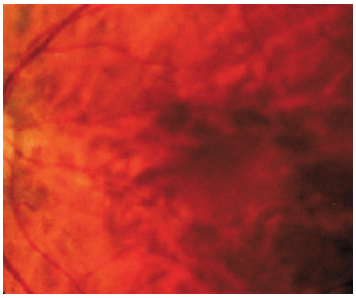
On SD-OCT, the RPE band is abruptly detached from Bruch's membrane and forms a regular, fairly prominent, rounded, gently sloping dome. The cavity appears to be optically empty with slight shadowing; the BM is just visible.

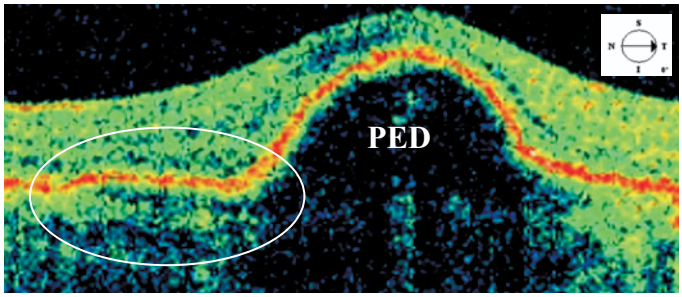
The external limiting membrane and IS/OS interface are clearly visible away from the lesion. They are less clearly visible over the PED but remain continuous.

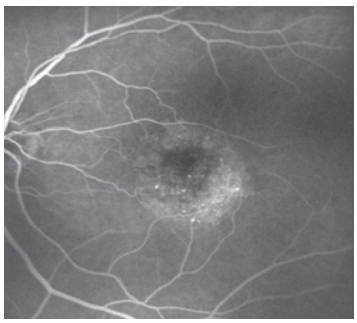
A hyper-reflective zone over the apex of the PED appears to displace retinal layers. A small zone of subretinal fluid is seen in the nasal sector.

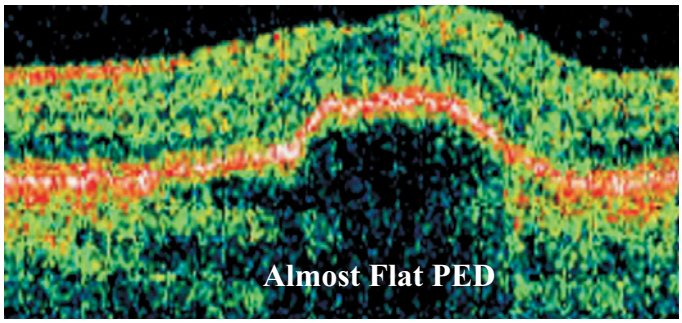
c): Enlargement of image (a): the BM is partially attenuated in the zone of the PED. It can nevertheless be identified below the regular and homogeneous RPE band, forming a dome over an optically empty cavity. This serous PED is related to the presence of occult CNV at its nasal margin (*circle*). It is associated with *inflammatory response signs,* mainly anterior to the RPE and at the level of the outer retinal layers.

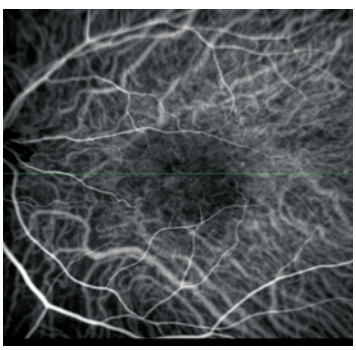
POSTERIOR TO THE RPE: SEROUS PED, FOLLOW-UP











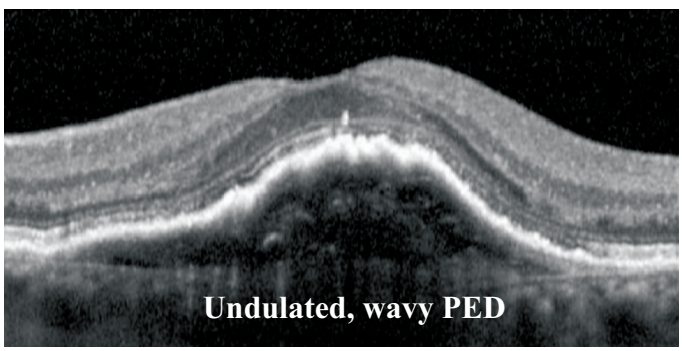


Figure 28: Elevation of the RPE: Very large serous PED associated with occult CNV–Good response to anti-VEGF therapy over a period of 10 months (VA 20/80 → 20/32).

***Stratus** and *Spectralis** horizontal sections associated with monochromatic or angiographic images.**

On **TD-OCT**, rounded, regular, fairly prominent gently sloping dome-shaped PED. The cavity appears to be optically empty with slight shadowing leaving the BM visible.

Various features may be observed during the course of a PED: the PED can gradually collapse and become less regular with wavy margins. The cavity might become slightly reflective, probably reflecting fibrous organization.

POSTERIOR TO THE RPE: FIBROVASCULAR PED

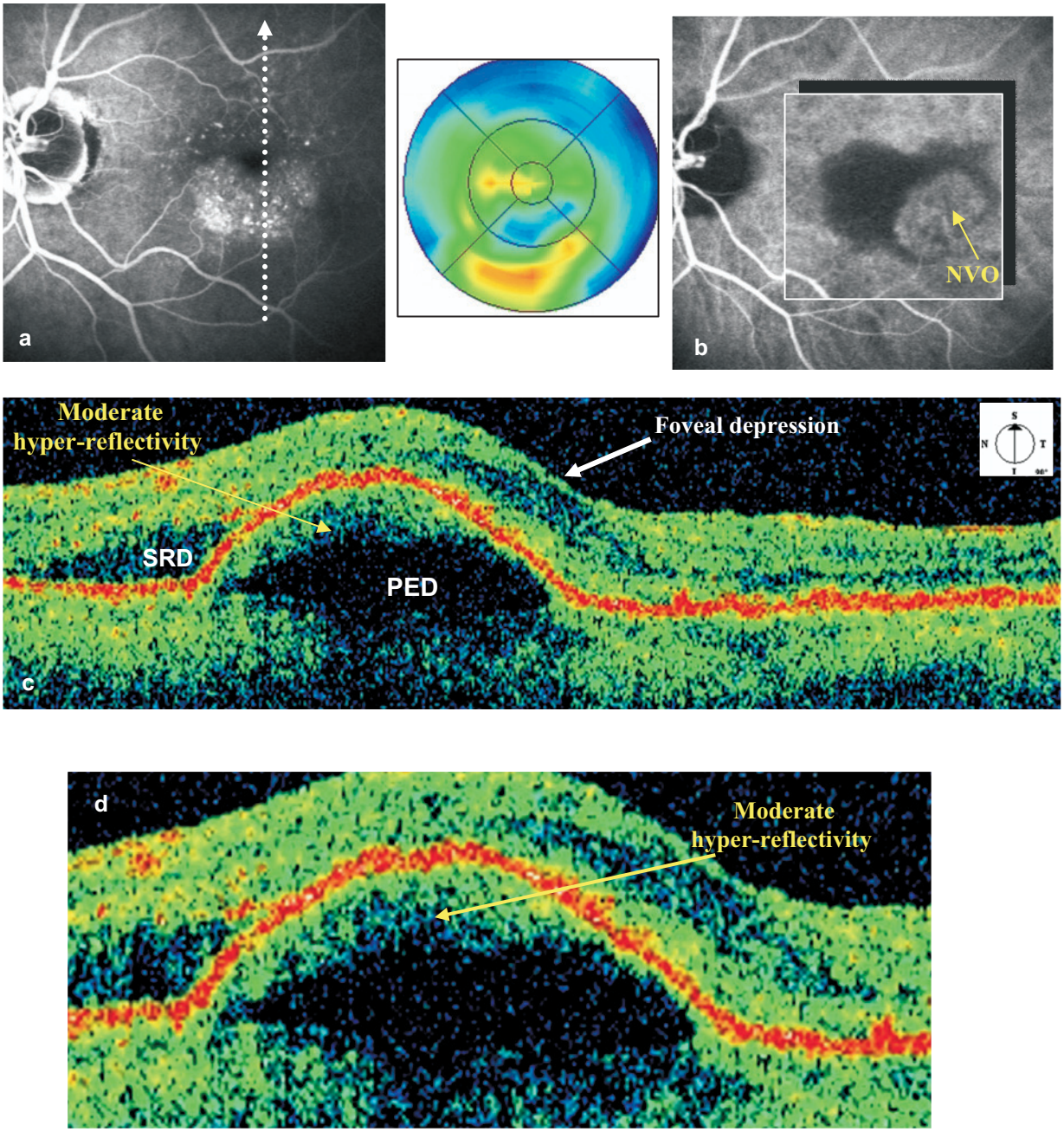


Figure 29: Elevation of the RPE: Vascularized PED partially invaded by occult CNV.

a and b): Fluorescein angiography and ICG angiography*: CNV clearly visible in the serous PED.*

c and d): *Stratus horizontal section.**

On **TD-OCT**, the RPE is hyper-reflective and clearly visible, raised in a very regular dome shape pattern with a mostly optically empty cavity.
The cavity is actually occupied by a moderately reflective band (*yellow arrow*) just posterior to the RPE, corresponding to the inferior part of the PED with CNV.

POSTERIOR TO THE RPE: FIBROVASCULAR PED

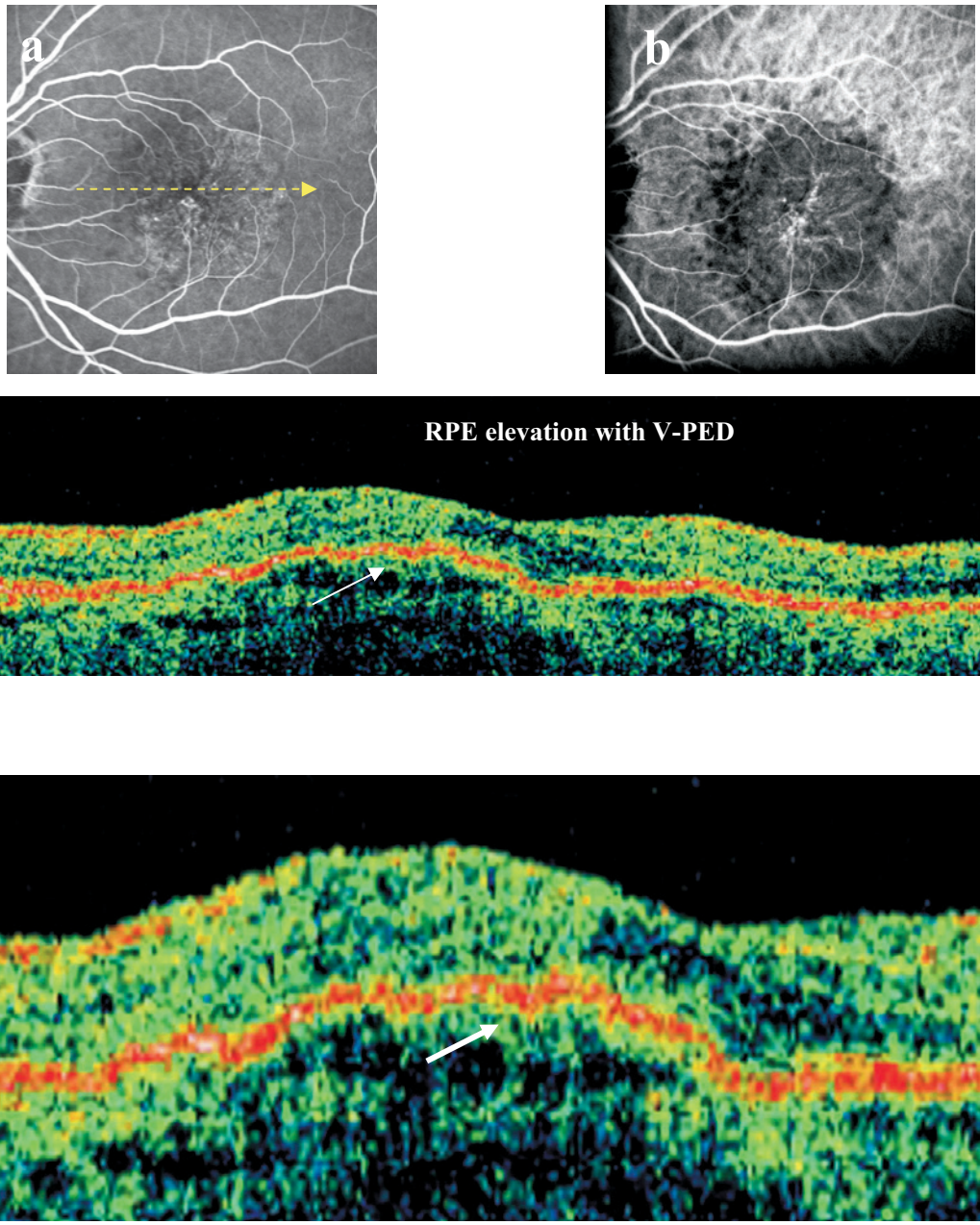


Figure 30: Elevation of the RPE: Fibrovascular PED associated with occult CNV (VA 20/80).

a and b): Fluorescein angiography and ICG angiography: *neovascular network invading all of the vascularized PED cavity.*

c and d): *Stratus horizontal section.**

On **TD-OCT**, the RPE is separated from the plane of Bruch's membrane (*arrow*) with a slight, heterogeneous elevation and partial shadowing. The cavity appears to be moderately reflective, suggesting partial organization.

d): Enlarged image (c): irregular thickness of the RPE and progressive fibrosis of the vascularized PED and intraretinal changes (infiltration and disorganization) reflecting the retinal reaction to choroidal neovascularization.

POSTERIOR TO THE RPE: FIBROVASCULAR PED

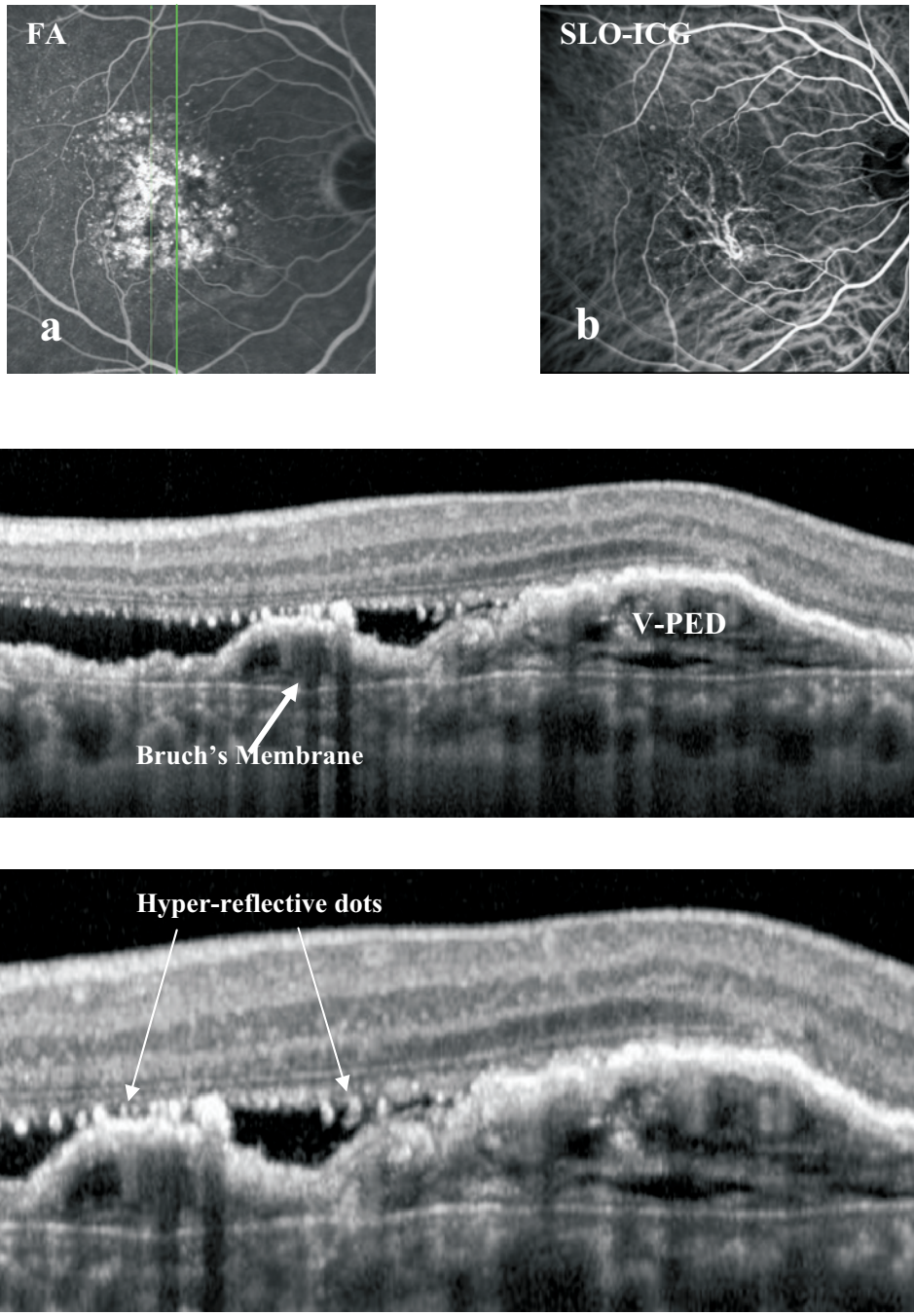


Figure 31: Elevation of the RPE: Fibrovascular PED associated with occult CNV.

a and b): Fluorescein angiography and ICG angiography: *CNV is clearly visualized on ICG angiography, invading all of the vascularized PED.*

c): *Spectralis vertical section:**

On SD-OCT, the RPE (irregular and thickened) is separated from Bruch's membrane (*arrow*) with a small heterogeneous elevation, corresponding to fibrovascular tissue and partial organization.
Spectral-Domain OCT demonstrates, not only persistence of subretinal fluid, but with hyper-reflective bright spots, which are a sign of activity (*double white arrows*). The preserved organization of inner and outer retinal layers is indicative of a favorable prognosis.

POSTERIOR TO THE RPE: ADVANCED FIBROVASCULAR PED

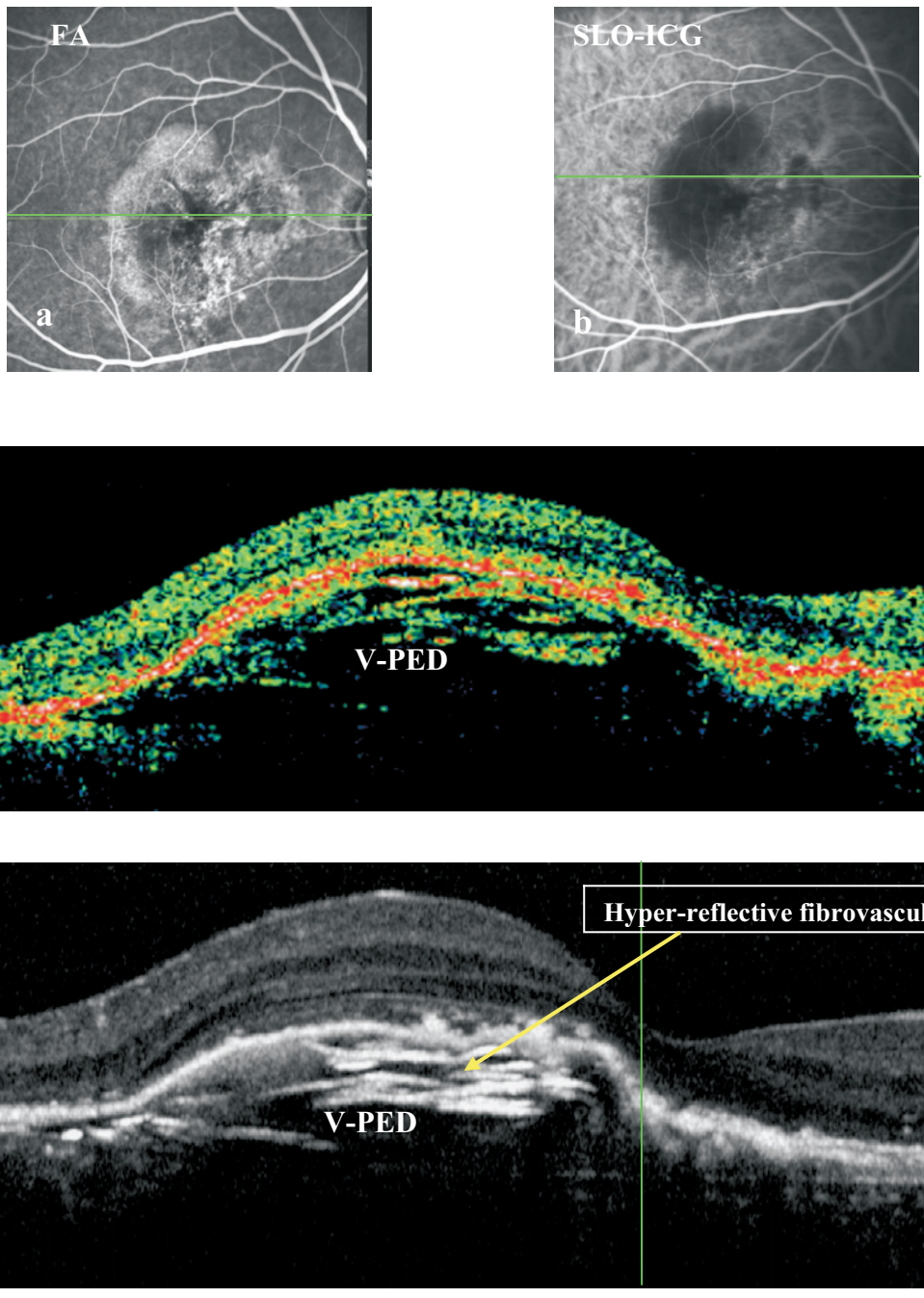


Figure 32: Elevation of the RPE: Advanced fibrovascular PED with extension of occult CNV and progressive fibrosis.

a and b): Fluorescein angiography and ICG angiography: *CNV is clearly visualized on ICG angiography, invading all of the vascularized PED.*

c): *Stratus horizontal section:** On TD-OCT, the elevated and bulging RPE delineates a cavity containing a large number of fibrous or fibrovascular elements with apparently little activity, inducing only moderate leakage, but more pronounced posterior shadowing.

d): *Spectralis horizontal section:** On SD-OCT, the hyper-reflective fibrovascular tissue is clearly visible with posterior shadowing. Note the irregularities of the RPE and slight alterations of the outer layers over the apex of the vascularized PED.

POSTERIOR TO THE RPE: PROGRESSIVE FIBROSIS

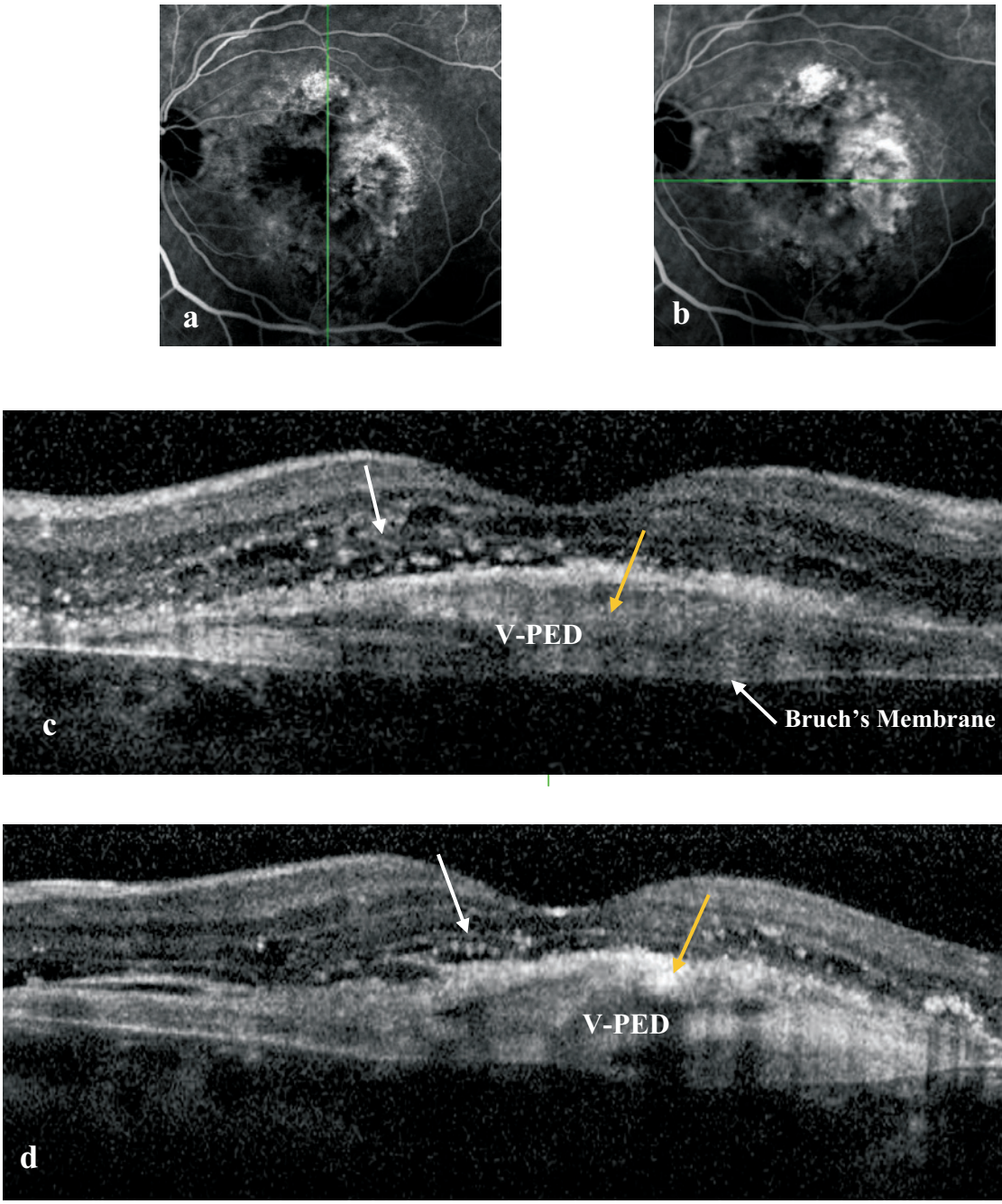


Figure 33: Elevation of the RPE: Progressive fibrosis posterior to the RPE.
a and b): Fluorescein angiography: *complex, extensive lesion, still active after 3 intravitreous injections.*
c): *Spectralis vertical section.**
On **SD-OCT**, the PED is flat but has a heterogeneous hyper-reflective cavity until Bruch's membrane, which remains visible. Despite this early fibrosis, the lesion is still active with fluid infiltration and numerous hyper-reflective bright spots (white arrow). Early signs of organization and probable fibrosis are seen.
d): *Spectralis horizontal section (same patient, after further treatment).**
The hyper-reflectivity posterior to the RPE (probable fibrosis) has increased. This progressive fibrosis is accompanied by resolution of the anterior reactive signs: decreased retinal thickness and hyper-reflective bright spots. The outer nuclear layer is barely visible, but organization of the other retinal layers is almost normal.

POSTERIOR TO THE RPE: FIBROTIC SCAR

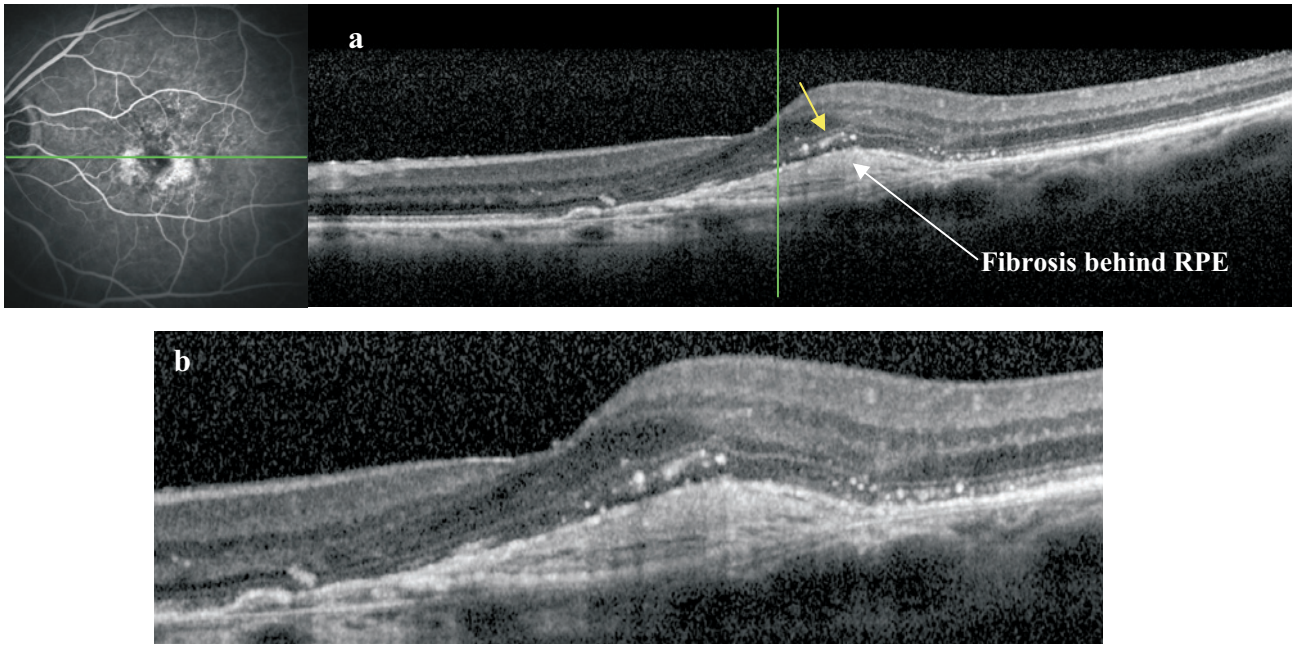


Figure 34: Elevation of the RPE: Fibrovascular PED, at the scarring stage, with fibrosis posterior to the RPE.
a): *Spectralis, horizontal section combined with fluorescein angiography** (*staining of the fibrotic lesion*).
On SD-OCT, the PED is relatively flat with a hyper-reflective, homogeneous cavity. Bruch's membrane remains slightly visible. After repeated intravitreous injections, the fibrovascular PED has become organized with probable fibrosis. There is no more fluid accumulation and the organization of the retinal layers has almost returned to normal.
b): Enlargement of the *Spectralis section (a):** The external limiting membrane is continuous but the IS/OS interface is altered with a few persistent bright hyper-reflective bright spots (*yellow arrow*); the outer nuclear layer is barely visible.

5. Posterior to the RPE: Shadowing or Hyper-Reflectivity

Pronounced hyper-reflectivity may be observed with *atrophy of the retinal layers* (or *post-laser atrophic scars*).

- This **atrophy** allows abnormal passage of light into the choroid. This hyper-reflectivity may immediately draw the examiner's attention.

- Atrophy of retinal layers in the central part of the fovea is mainly observed in advanced forms, either spontaneously or after treatment. In these cases, pronounced thinning of the neurosensory retina allows increased passage of light (**Figure 35**).

- Atrophy of the RPE may also be associated with resorption of lipofuscin deposits (**Figure 8**), a previous RPE tear (**Figure 9**), or laser treatment (**Figure 36**).

Inversely, the presence of various *hyper-reflective structures in the inner retinal layers* can also cause changes on OCT.

- These alterations can induce **back-shadowing**, which may extend posteriorly to the choroid, when no light penetrates into this layer.

This is the case with retinal hemorrhage, accumulation of material, or classic CNV (**Figures 37-40**).

Similarly, lipid exudates (**Figure 41**), large retinal vessels, or dense clumps of pigment can induce back shadowing, even until the level of the choroid (**Figures 42 and 43**).

POSTERIOR TO THE RPE: HYPER-REFLECTIVITY AND SHADOWING

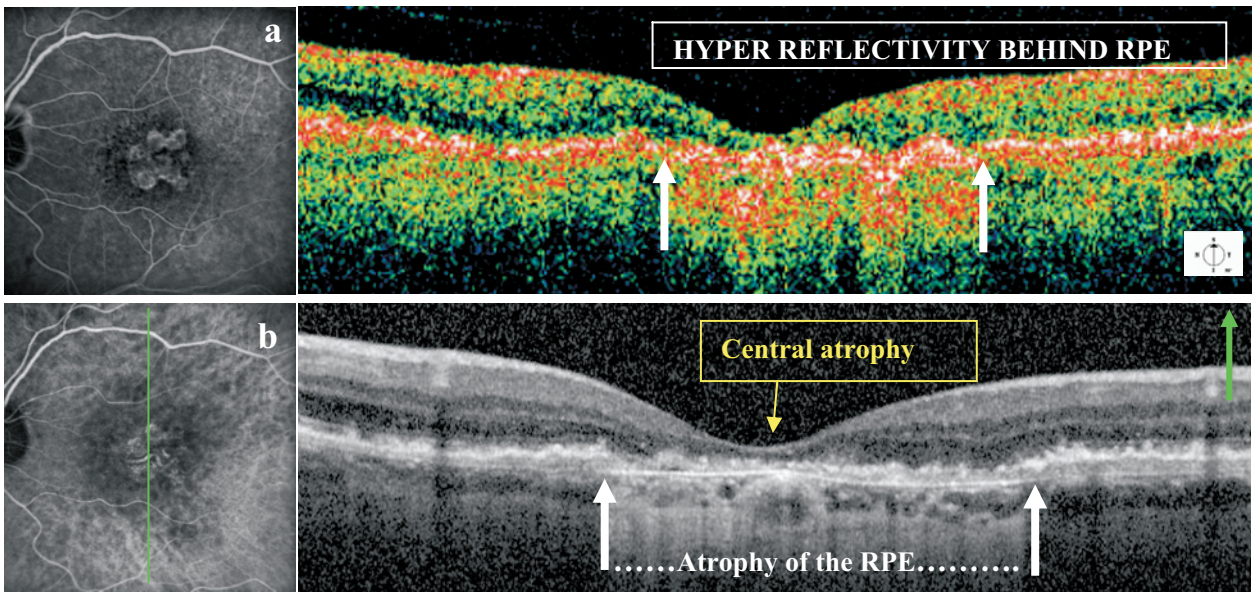
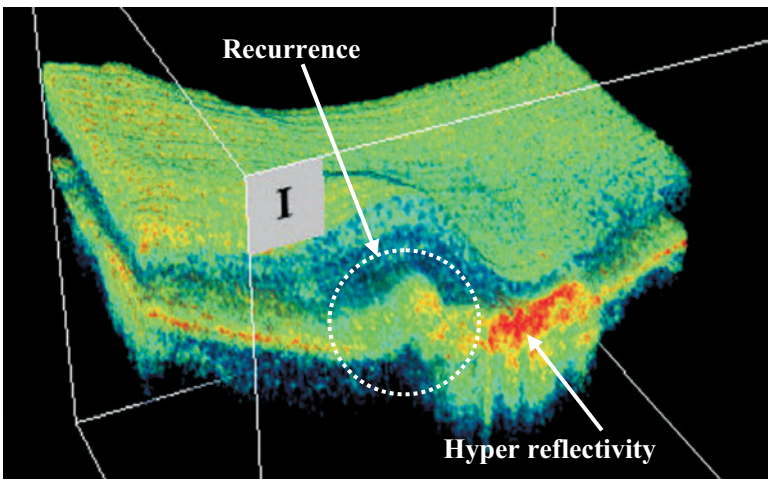


Figure 35: Posterior hyper-reflectivity due to atrophy of the neurosensory retina.

a): *Stratus vertical section correlated with fluorescein angiography** (*geographic atrophy due to resorption of drusen).*

b): *Spectralis vertical section combined with ICG angiography** (*same patient*). Thinning of the central neurosensory retina is associated with atrophy of the RPE and pronounced hyper-reflectivity towards the choroid. Note the loss of the outer retinal layers in the atrophic area.



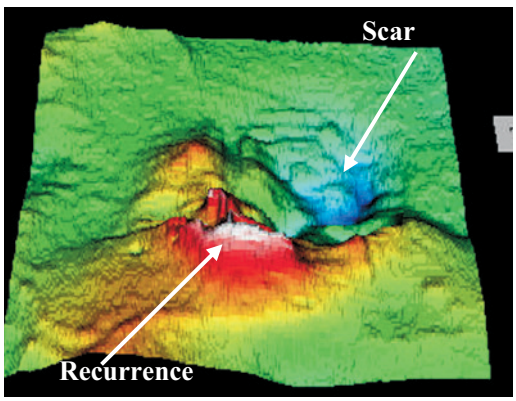


Figure 36: Posterior hyper-reflectivity due to post-laser atrophy.

***Topcon** 3D volume and surface mapping section**: post-laser atrophy and adjacent subfoveal recurrence.

The laser scar causes posterior hyper-reflectivity and thinning on retinal mapping, reflected by a blue color.
The hyper-reflectivity in choroidal layers is clearly visible and is associated with an atrophy, not only of the RPE, but also of the neurosensory retina. The can be seen particularly in the central foveal zone, which accounts for the irreversible loss of VA (20/100).

POSTERIOR TO THE RPE: MASKING BY HEMORRHAGE

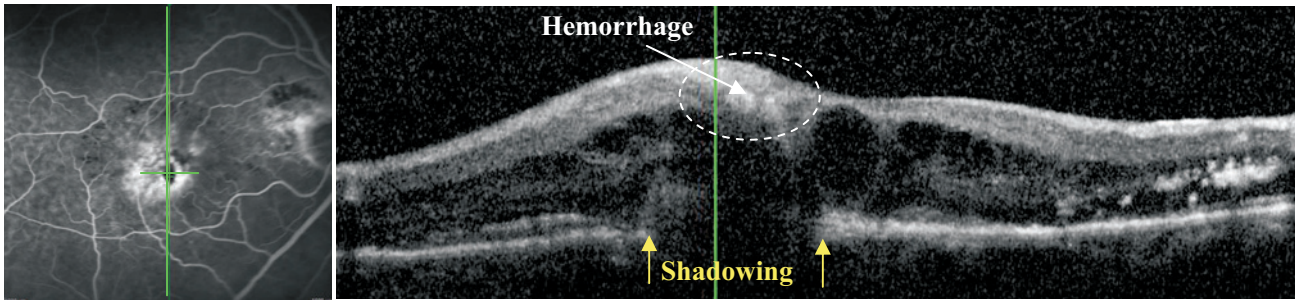


Figure 37: Localized masking of the RPE due to the presence of retinal hemorrhage.

***Spectralis** vertical section combined with fluorescein angiography**: *localized hyper-fluorescence partially masked by dense and superficial retinal hemorrhage.*

Hemorrhage causes posterior shadowing which masks not only the RPE, but also all intraretinal structures and features posteriorly, such as the choroid.

POSTERIOR TO RPE: MASKING BY DEEP HEMORRHAGE

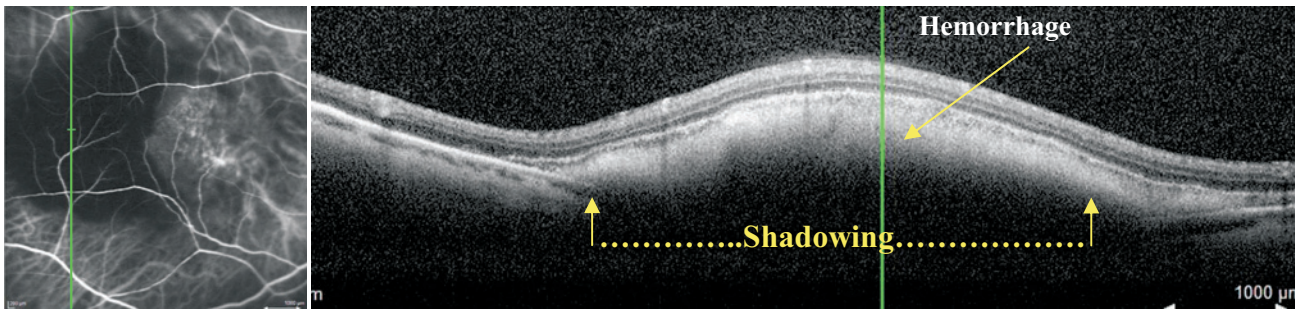


Figure 38: Localized masking of the RPE due to the presence of a large hemorrhagic detachment of the RPE.

***Spectralis** vertical section combined with ICG angiography**: *marked hypo-fluorescence corresponding to the hemorrhage adjacent to a deep neovascular network visible in the PED.*

Hemorrhage induces pronounced hyper-reflectivity with major shadowing, as the light does not penetrate through the layers of blood. This induces posterior masking not only of Bruch's membrane but of all posterior structures including the choroid.

POSTERIOR TO THE RPE: SHADOWING BY MATERIAL

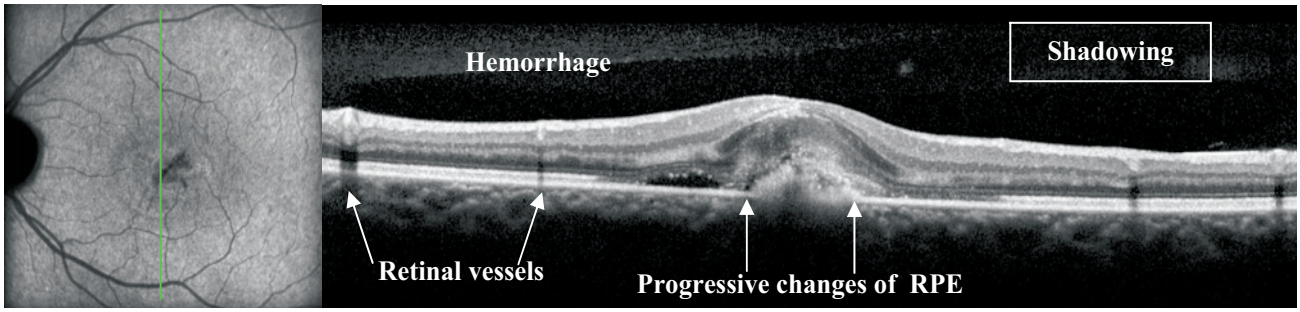


Figure 39: Partial masking of the RPE related to the presence of lipofuscin deposits.

***Spectralis** vertical section combined with ICG angiography, late phase**: *the material remains markedly hypo-fluorescent.*

On **SD-OCT**, the material accumulated in front of the RPE is cone-shaped with maximum thickness in the center, corresponding to maximum masking of the RPE. The RPE remains visible, although attenuated on either side.

Note that the large vessels of the superior and inferior temporal arcades causes clearly visible and well-defined shadowing from peripheral layers (the site of the vessels) towards the choroid.

POSTERIOR TO THE RPE: LOCALIZED MASKING BY NEOVASCULARIZATION

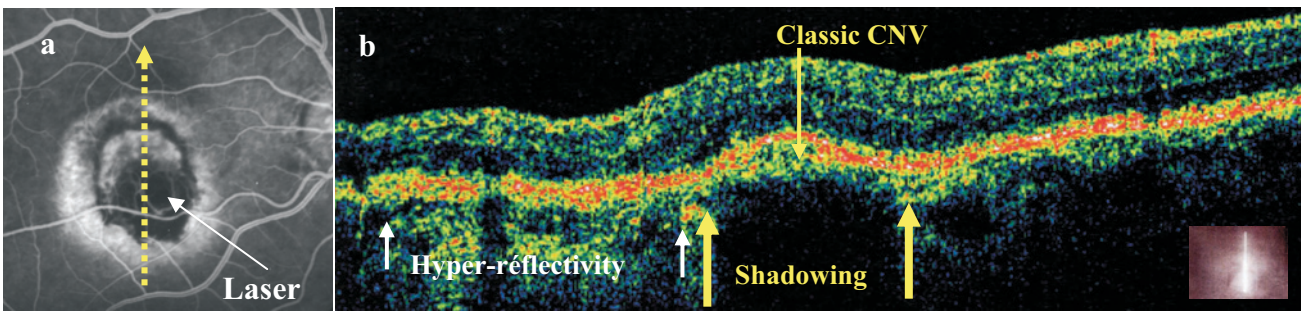


Figure 40: Shadowing with masking of the RPE, related to the presence of classic CNV.

a): Fluorescein angiography: *inferior parafoveal laser scar and recurrence of classic CNV on its superior edge.*

b): *Stratus vertical section.**

The **TD-OCT** section initially passes through the inferior scar, causing marked posterior hyper-reflectivity. The section then passes through the recurrent CNV on the superior edge of the scar: CNV induces a bulging cone-shaped zone of hyper-reflectivity accompanied by posterior shadowing.

POSTERIOR TO THE RPE: LOCALIZED MASKING BY LIPID EXUDATES

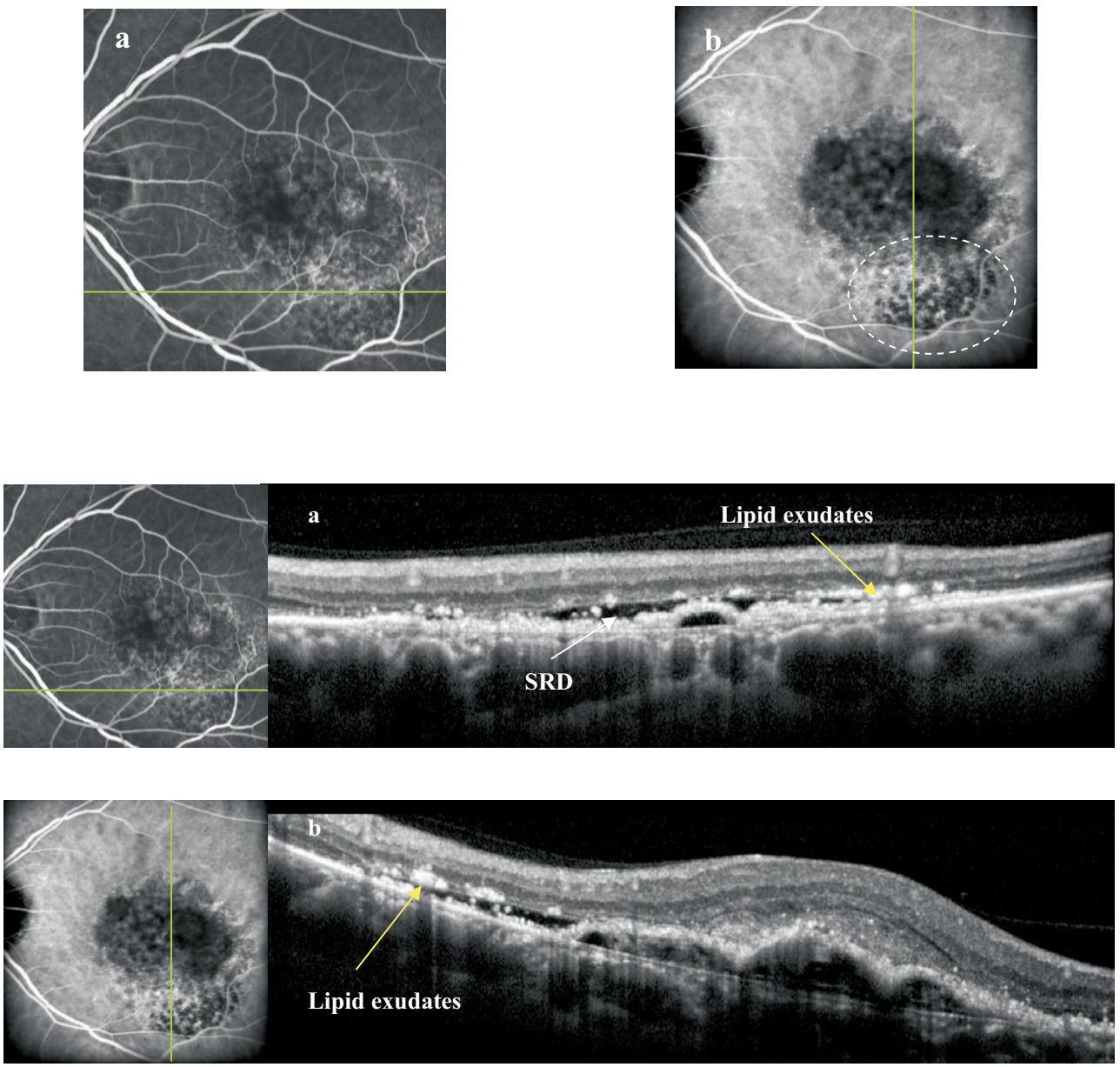


Figure 41: Shadowing related to the presence of lipid exudates at the periphery of CNV.

a): *Spectralis horizontal section combined with fluorescein angiography** (*extensive occult CNV with serous retinal detachment and accumulation of exudates at its inferior edge).*

On **SD-OCT**, exudates are seen as tightly packed hyper-reflective clumps in the outermost layers of the retina.

This is similar to the hyper-reflective bright spots usually associated with active CNV (as in the more temporal zone of the section).

b): *Spectralis vertical section combined with ICG angiography** (*same patient*): Similar appearance of lipid exudates in the outer layers of the retina.

POSTERIOR TO THE RPE: LOCALIZED MASKING BY NORMAL RETINAL VESSELS

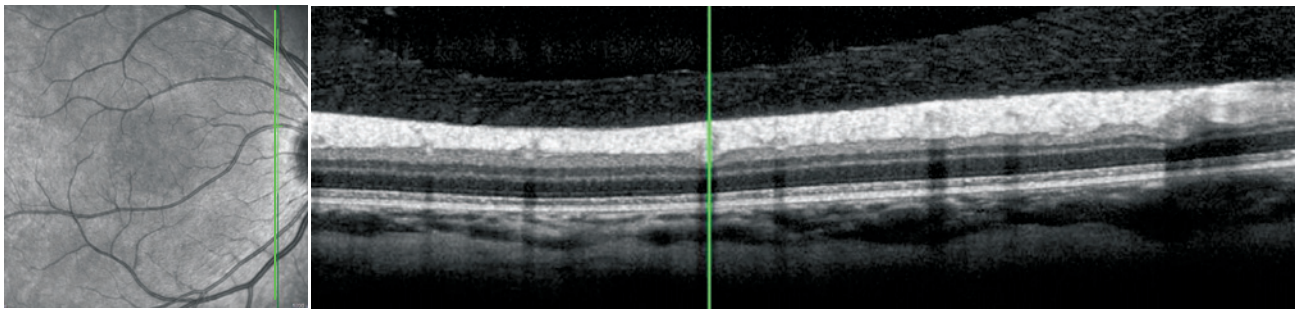


Figure 42: Shadowing by retinal vessels.

***Spectralis** vertical section combined with a reference red-free image**.

The **SD-OCT** section passes adjacent to the optic disc and shows the large retinal vessels.

These vessels are clearly visible and induce a small zone of hyper-reflectivity followed by masking over a narrow zone, which corresponds to the diameter of the vessel. The effect crosses all layers of the retina even until the RPE and choroid. The vessel's walls are usually highly reflective.

In some cases, it is even possible to distinguish the vessel lumen and its associated backward-masking in the outer layers.
This type of masking is easily recognized and is often used as a landmark for comparison with angiography.

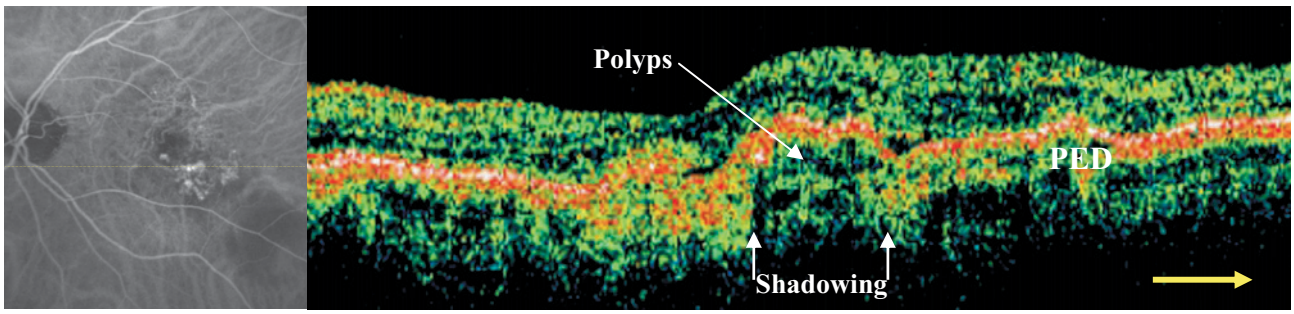


Figure 43: Shadowing induced by the presence of polypoidal formations.

***Stratus** horizontal section shown with ICG angiography** (*clearly demonstrating very dense polyps, the normal choroidal network, and the inferior macular PED).*

On **TD-OCT**, this is immediately suggestive with the steeply sloped multi-lobed prominence, which lifts the RPE and induces relative posterior masking.
The superior pole of the PED is visible and continues temporally.
Also note the subfoveal fibrosis inducing posterior hyper-reflectivity.

III. Anterior to the RPE Band

TD-OCT

Reactive signs related to the presence of different features of AMD, either *precursors* or *complications* (atrophic or neovascular), can gradually accumulate.

- **Fluid accumulation** is the most easily detectable and quantifiable sign in exudative AMD and is therefore routinely evaluated. It essentially corresponds to *intraretinal* or *subretinal* fluid infiltration and accumulation.

These intraretinal fluid collections can be *diffuse* or associated with *cystoid spaces*. Cystoid spaces can progress to become more numerous, larger, and eventually confluent, especially in the central foveolar zone.

The **inner layers** of the retina are only slightly modified in the early stages, but subsequently become disorganized due to fluid infiltration and an inflammatory response.

The various stages of AMD along with the indications for and results of treatment are often assessed based on the amount of leakage.

This leakage appears *easy to evaluate and quantify* on OCT, at least in terms of fluid accumulation and retinal thickness, which are measureable.

- **Central retinal thickness** (CRT) is certainly an easy criterion to use, but it is not sufficient to fully describe the polymorphous clinical forms of AMD and their course.

- Hyper-reflective **pre-retinal vascular proliferations** can be fairly easy to identify and localize, but they must be clearly distinguished from accumulation of non-vascular material or fibrin deposits, which appear as part of the healing process.

More extensive imaging and particularly angiography is essential in these situations.

SD-OCT

- **Other reactive signs** can now be appreciated on OCT with the advent of Spectral-Domain technology.

These advantages are most apparent when evaluating the outer retinal layers (*outer nuclear layer, external limiting membrane, photoreceptor cell bodies, and inner segment/outer segment interface*).

- Additional signs appear to reflect the presence of active CNV, their abnormal permeability, and the inflammatory response they elicit. These signs include:
  - *Bright hyper-reflective* spots adjacent to fluid and outer layers but sometimes disseminated as far as the inner layers.
  - *Dense zones with enhanced reflectivity*, displacing or spreading inside the outer nuclear layer and sometimes extending as far as the inner layers.

1. Fluid Accumulation Anterior to the RPE: Sub-Retinal Detachments (SRD)

The presence of serous fluid is visualized as a homogeneous optically empty space, and therefore is hyporeflective and dark on OCT images. The space situated between the neurosensory retina and the RPE is an **easily detachable potential space**. Any abnormal exudation can accumulate in this space and create a serous detachment of the neurosensory retina (SRD).
During the course of disease, the size of the SRD can progressively change. The SRD is sometimes minimal and limited to a barely visible thin layer of fluid, which is usually associated with a highly suggestive localized intraretinal infiltration. (**Figure 44**).

Active CNV causes more marked leakage, creating a more elevated SRD, which is usually also associated with intraretinal cysts (**Figure 45**).
When the retina is already raised by a serous detachment of the RPE, fluid accumulation anterior to the RPE appears to be limited to or localized around the PED and therefore has a fairly characteristic triangular shape on OCT cross-sections (**Figure 46**).
Diverse changes in the relative degree of fluid accumulation under the neurosensory retina (ie, SRD), RPE (ie, PED), or intraretinal cysts may be observed during the subsequent course of disease.

MINIMAL SRD

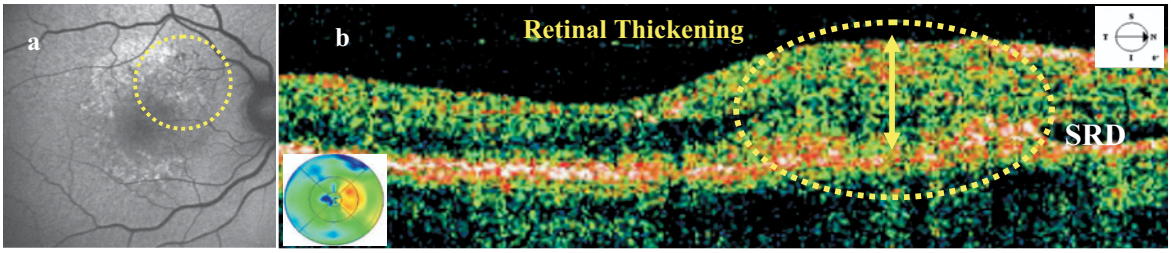


Figure 44: Fluid accumulation anterior to the RPE with minimal SRD.
a) Autofluorescence: multiple perifoveal hyperfluorescent areas.
b) *Stratus TD-OCT horizontal section**: early lesion in the nasal and superior sectors of the fovea with intraretinal fluid accumulation and increased retinal thickness (*circle*) associated with a limited adjacent SRD.

MODERATE SRD

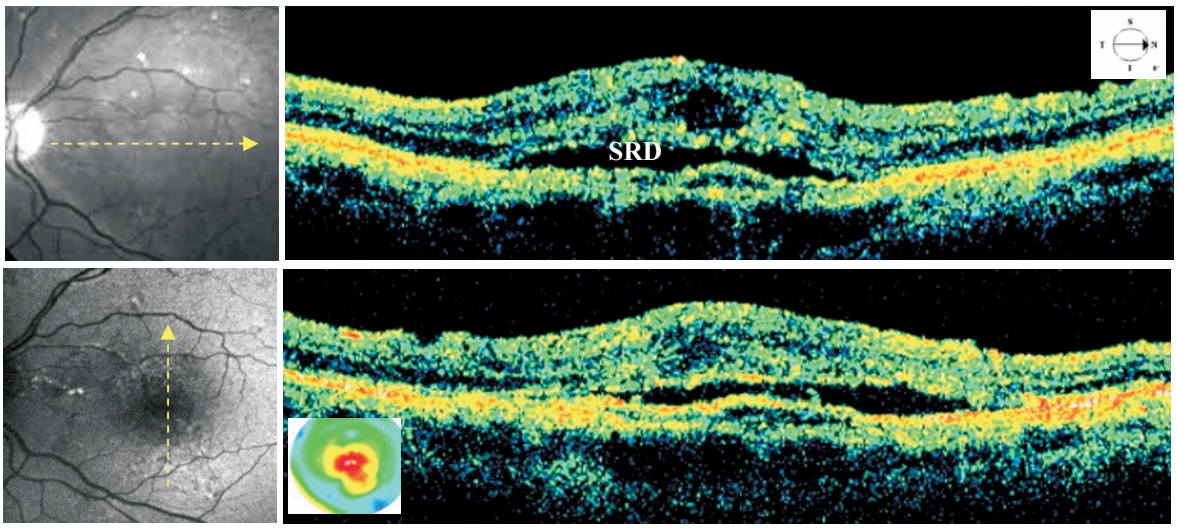


Figure 45: Fluid accumulation anterior to the RPE.
***Stratus** horizontal and vertical sections correlated to red-free and autofluorescence images.**
This OCT section demonstrates elevation of the macular region with loss of the foveal depression.
The SRD is an optically empty, black spindle-shaped zone between the RPE and neurosensory retina.
Anteriorly, the retina is thickened and infiltrated with a large central cyst, but retains an almost normal configuration.
Posteriorly, a PED can be seen, suggesting the presence of an occult CNV.

SRD ASSOCIATED WITH A PED

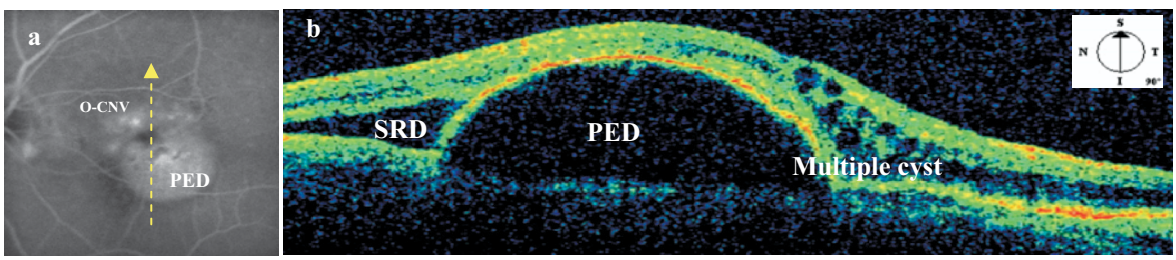


Figure 46: Fluid accumulation anterior to the RPE associated with a serous PED.
a): Fluorescein angiography: serous PED with a small area of occult CNV at its superior edge.
b): *Stratus OCT vertical section**: dome-shaped elevation of the RPE related to the serous PED.
In the inferior part, localized, triangular SRD with fluid accumulation anterior to the RPE. In the superior part, multiple cysts and intraretinal fluid. At the summit of the dome of the PED, the retina is in contact with the RPE and has a normal thickness.

2. Fluid Accumulation Anterior to the RPE

Features of SRD and its Evolution

Active choroidal neovascularization is accompanied by enlargement of the serous retinal detachment (SRD), with frequent shifting of subretinal fluid.

The presence and size of serous retinal detachment must therefore be studied completely on serial sections of the macula (**Figure 47**).

Regression of the SRD

Rapid regression of the SRD, particularly after the first injections of anti-VEGF, suggests treatment efficacy and is also generally accompanied by a rapid and marked functional improvement.

This regression then becomes slower, decreasing intraretinal fluid and cysts but leaving a limited yet persistent band of SRD.

The subretinal detachment may even paradoxically increase, followed later by gradual regression (**Figures 48-50**).

Persistent Fluid

The fluid layer of the SRD sometimes *chronically* persists. This occurs especially when treatment is delayed and fibrosis has already begun (**Figures 51 and 52**).

Persistent fluid is sometimes compatible with a relatively stable and fair visual acuity if subretinal fibrosis remains moderate. In this situation, the presence of subretinal fluid is not an absolute indication for retreatment (**Figure 53**).

Complications

Some complications are often associated with (recurrent) exudative lesions. The presence of a limited SRD, detectable only on OCT sections, may explain the occurrence of symptoms such as metamorphopsias and decreased visual acuity.

This could detect early recurrences of CNV for example at the edge of a known laser scar (**Figures 54 and 55**).

Extensive leakage may also be observed in cases of RPE tears, mainly from the exposed choriocapillaris (**Figure 56**) or in cases of active occult CNV (**Figure 57**).

The incidence of SRD is lower than that usually reported.

SRD is not a constant feature in early forms of AMD or during a stable course, but it is often a sign of active disease.

The thickness of the SRD usually remains moderate or limited, and the SRD is often only discovered on vertical sections or sections of the inferior part of the macula.

In a study of 150 consecutive cases of wet AMD, SRD was present in only 28% of eyes.

The SRD was more clearly visible or more accentuated in the prone position and on vertical sections in two-thirds of cases.

The SRD was associated with cystoid spaces in one-half of cases.

The SRD was minimal (defined as an increase of less than 100 µm) in one-third of cases (30%); moderate (increase of 100 to 200 µm) in about one half of cases (45%); and marked (increase greater than 200 µm) in only a quarter of cases (25%).

The SRD regressed in response to treatment, but persisted to a lesser extent in 80% of cases after three intravitreous injections of anti-VEGF, (minimal in 25% of cases, moderate in 44% of cases, and marked in 31% of cases of persistent SRD).

Conversely, diffuse intraretinal fluid or intraretinal cysts (with variable shape and volume) appear to be much more frequent and are more often responsible for the increased central retinal thickness.

PREDOMINANTLY SHIFTING SRD

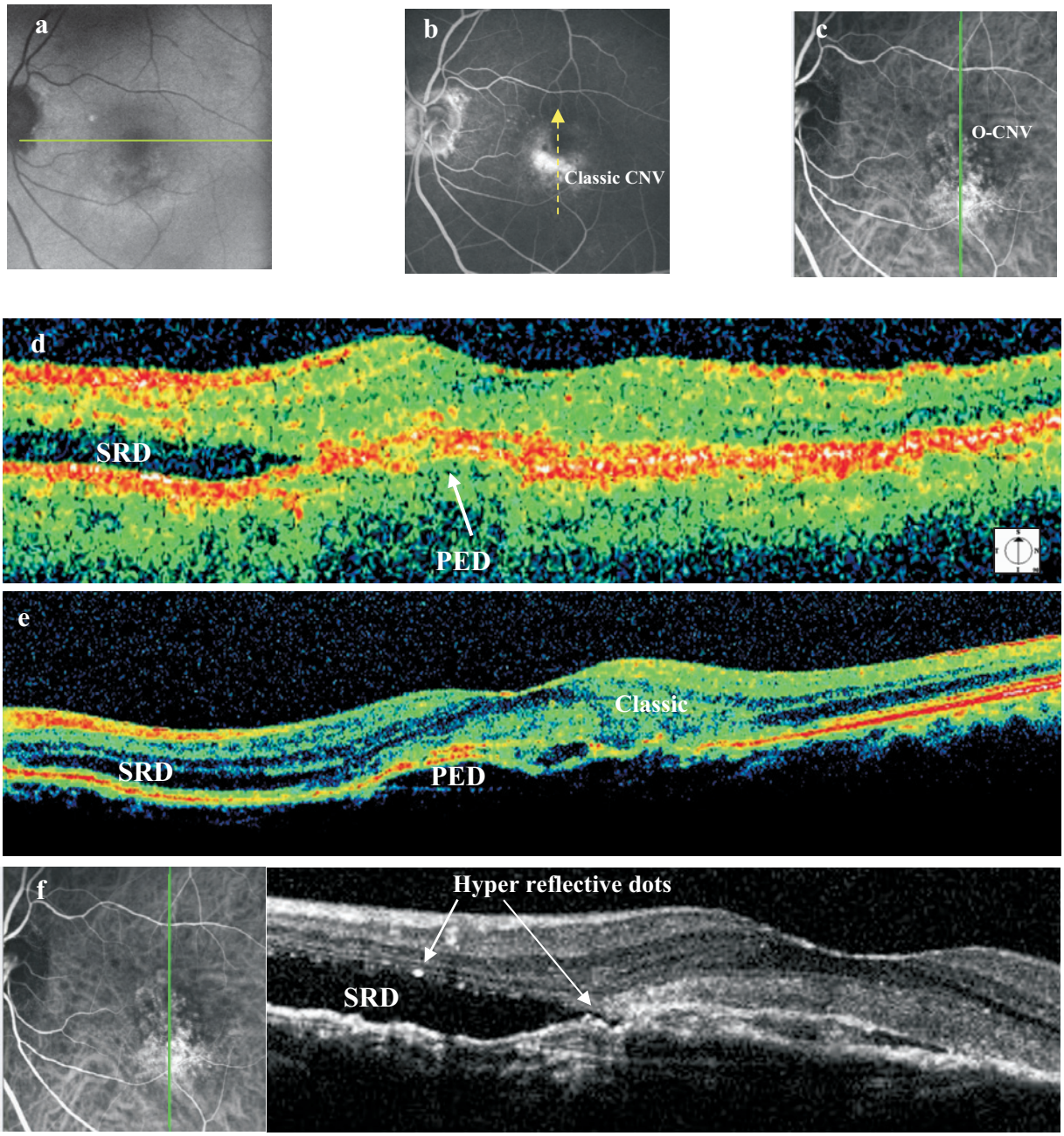


Figure 47: Fluid accumulation anterior to the RPE associated with advanced occult CNV.
a, b, and c): Autofluorescence, fluorescein angiography, and ICG angiography *(mixed, occult, and classic CNV).*
d): *Stratus OCT vertical section**: relatively marked SRD but limited to the inferior foveal region. The central retina appears slightly thickened but with no cysts. The hyper-reflective zone anterior to the RPE is suggestive of the presence of classic CNV. Note the flat PED with thickening of the RPE.
e): *Spectralis 110° vertical section** demonstrating the profile of the lesion with subfoveal mixed CNV and an inferior SRD.
f): Enlarged image associated with ICG angiography *(showing the real extent of the lesion).*
On SD-OCT, the SRD is even more clearly visible. Note the bright hyper-reflective spots on the internal limits of the SRD. They are probably reflecting active inflammatory response and damage to outer segments.
The external limiting membrane is still visible on all cross-sections. Note many irregularities on the RPE band. Bruch's membrane is clearly visible delimitating a partially organized PED.
In the subfoveal area, between the external limiting membrane and the RPE, there is a relatively dense and thick material which appears to occupy or surround the IS/OS interface, which is probably an inflammatory response around classic CNV.

PARTIAL REABSORPTION OF SRD

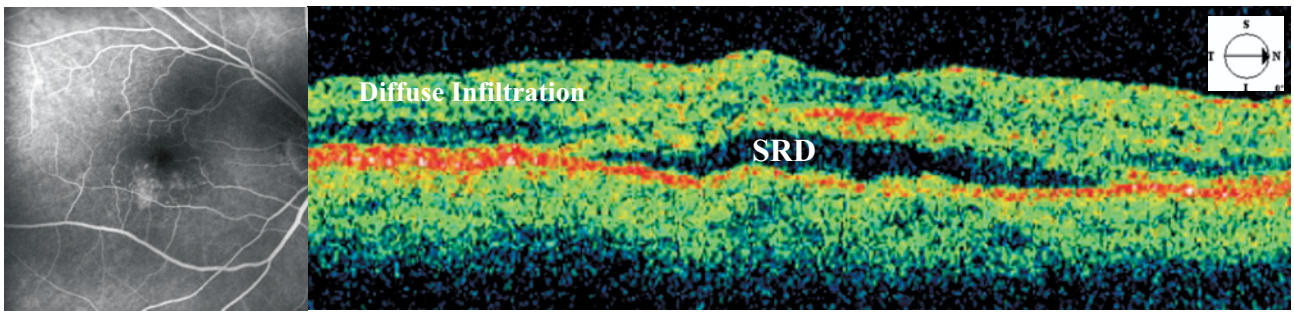


Figure 48: Fluid accumulation anterior to the RPE, resolving after treatment.

***Stratus** horizontal section associated with fluorescein angiography** *(showing resolution of occult CNV).*

The TD-OCT horizontal section shows a clearly visible subfoveal SRD. The central retina is still slightly thickened, with a visible but flattened foveal depression without any cystoid edema.
The SRD is not completely optically empty, but presents minimal hyper-reflectivity, possibly related to the presence of proteins.

PARTIALLY RESOLVED SRD

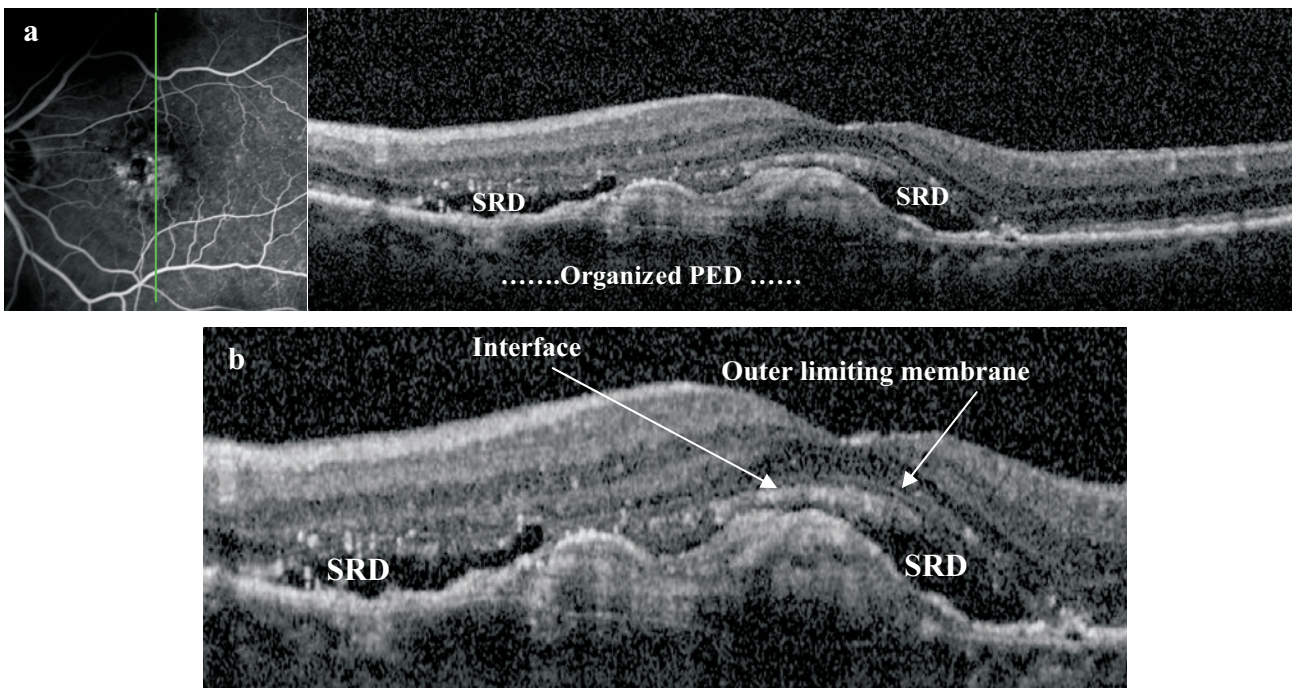


Figure 49: Fluid accumulation anterior to the RPE, partially resolved after treatment.

a): *Spectralis vertical section associated with fluorescein angiography** *(persistence of an area of occult CNV with moderate leakage).*
The OCT section shows persistence of the SRD anterior to a wavy and partially organized vascularized PED.

b): Enlarged view: despite improvement in response to treatment, the SRD and its limits are still marked by many bright hyper-reflective spots. The IS/OS interface is discontinuous but thickened in the subfoveal zone. The outer nuclear layer remains thinned and irregular, except in the subfoveal zone. The external limiting membrane is clearly visible and continuous, and the other retinal layers appear to be well-organized.

RESIDUAL SRD IN THE INFERIOR ZONE

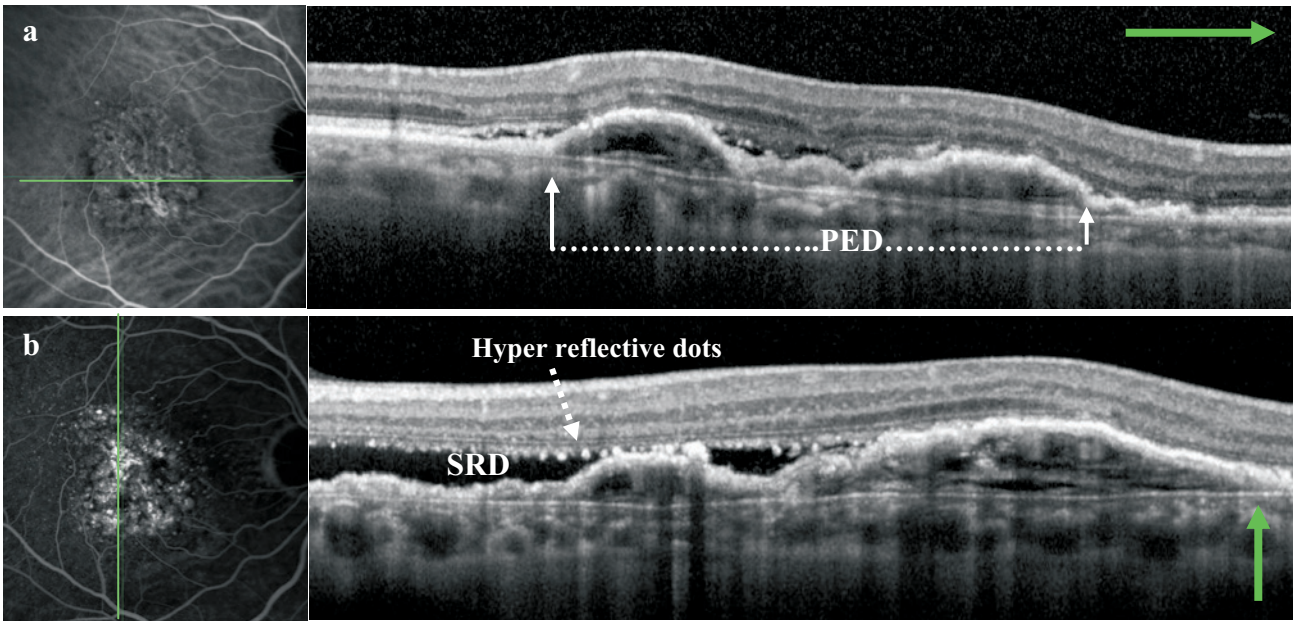


Figure 50: Fluid accumulation anterior to the RPE, partially resolved after treatment.

a): Spectralis* horizontal section, associated with ICG angiography *(persistence of the neovascular network).*
On SD-OCT, the SRD has almost completely resolved but persists at the edges and between the different domes of the vascularized PED.

b): *Spectralis vertical section, associated with fluorescein angiography.**
SD-OCT also shows persistence of shifting intraretinal fluid, and then, only visible on the vertical section. Note the multiple bright hyper-reflective spots at the edges of the SRD.

LONG DURATION SRD

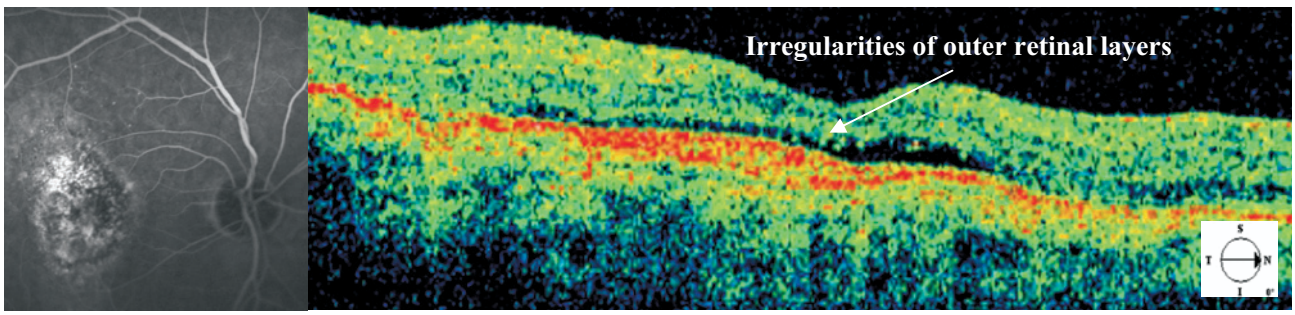
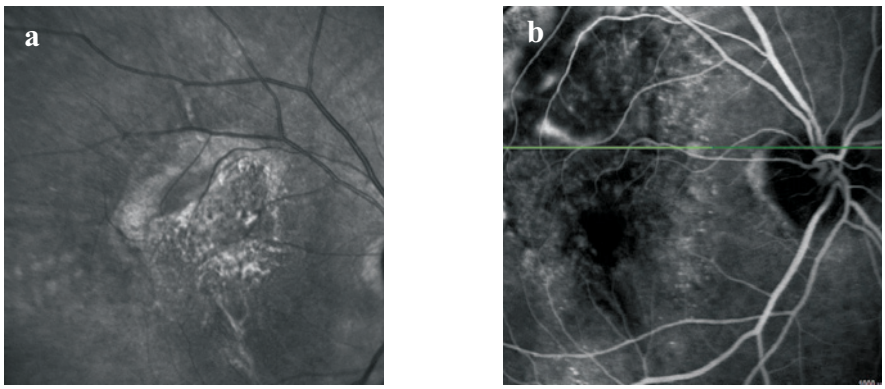


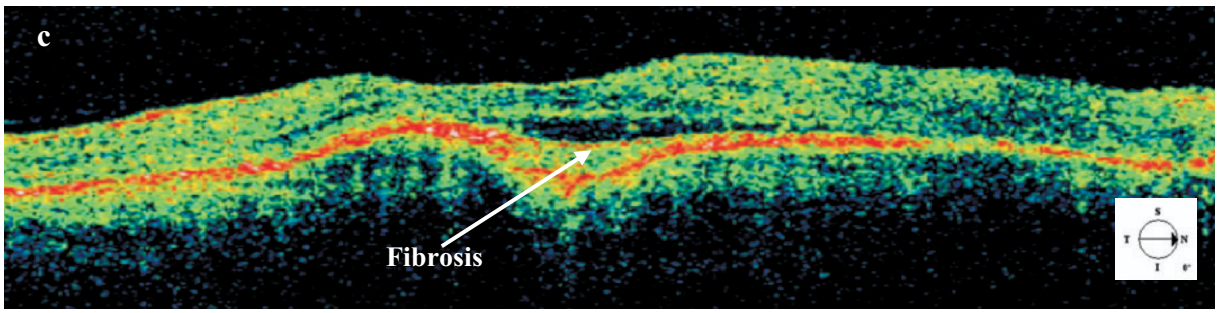
Figure 51: Fluid accumulation anterior to the RPE, partially resolved after multiple treatments.

***Stratus** horizontal section correlated with fluorescein angiography**: some leakage is still visible.

On TD-OCT, ongoing fibrosis (hyper-reflective band) associated with a thin layer of fluid anterior to this fibrosis.
Note the multiple irregularities of the photoreceptors often observed in chronic SRD.

LONG DURATION SRD WITH FIBROSIS





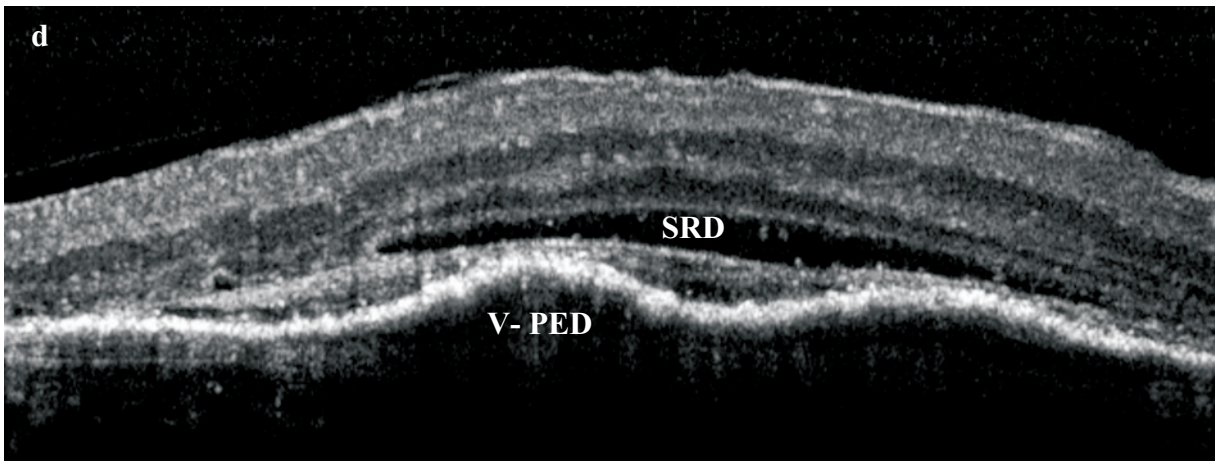


Figure 52: Fluid accumulation anterior to the RPE, persistent and chronic after treatment.

a and b): Red-free photography and fluorescein angiography: old vascularized PED in the process of healing with retraction towards the central fibrosis. The lesion is still thick and raised.

c): *Stratus horizontal section.**
On TD-OCT, a layer of moderately reflective fibrosis has formed anterior to the residual PED. A moderately thick SRD persists over this fibrosis, despite the absence of intraretinal fluid.

d): *Spectralis horizontal section.**
On SD-OCT, a small persistent pseudo-cystic space is visible between the IS/OS interface (persistent fluid) and the fibrous tissue that has proliferated anterior to the RPE band. The vascularized PED has become almost completely flattened.
The different outer retinal layers are disorganized and poorly distinguishable.

MINIMAL PERSISTENT SRD

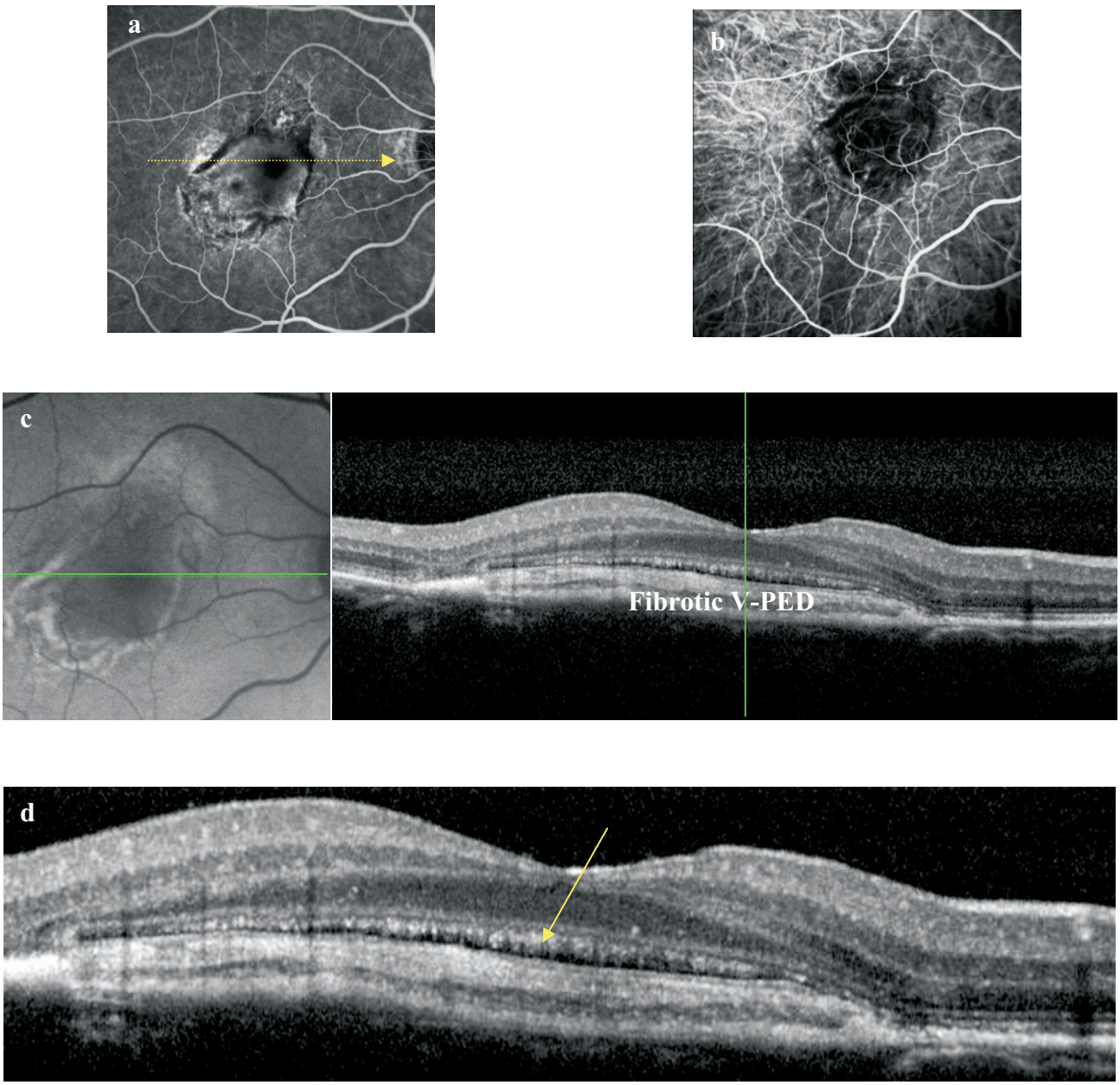


Figure 53: Chronic fluid accumulation anterior to the RPE persisting after treatment.

a and b): Fluorescein and ICG angiography: retracted and fibrotic classic CNV membrane.

c): *Spectralis horizontal section, associated with autofluorescence image.**
On SD-OCT, anterior to the residual organized and hyper-reflective PED, there is a limited but persistent layer of fluid. Many bright hyper-reflective spots (*arrow*) are visible at the outer limit of the retina and also a few disseminated in all of the layers.

d): Enlarged view: the IS/OS interface and external limiting membrane remain visible and continuous. The other nuclear layer, the plexiform layers and the foveal depression remain well organized. This is well correlated with the fair visual acuity (20/32).

RECURRENCE AND SRD

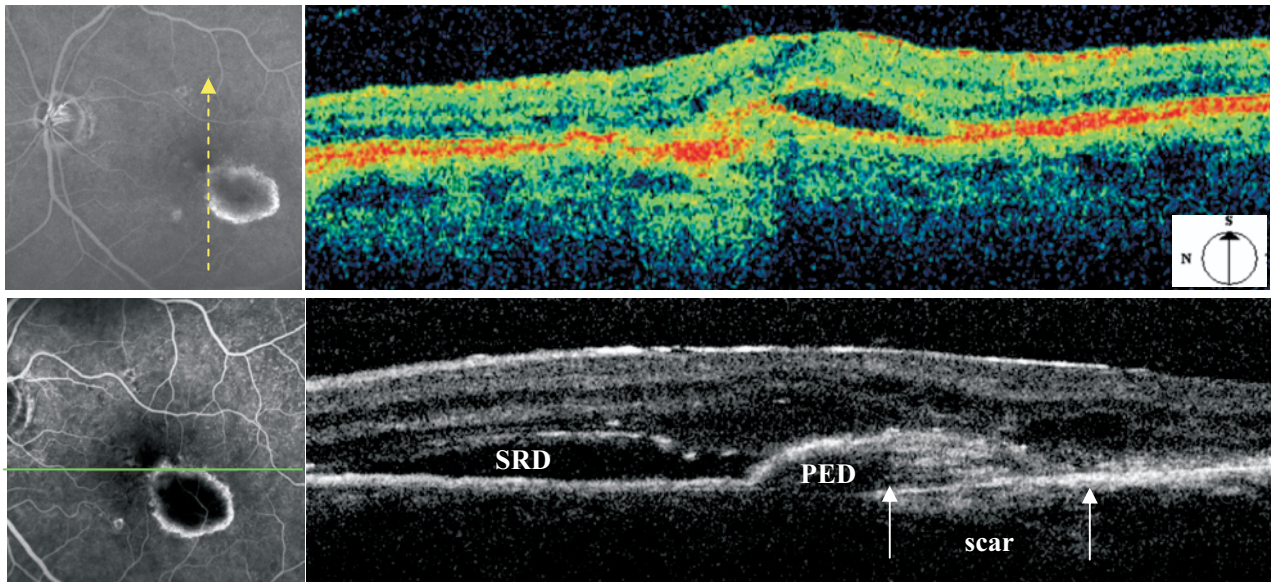


Figure 54: Recent fluid accumulation anterior to the RPE suggesting a juxtafoveal recurrence.

***Stratus** vertical section, associated with fluorescein angiography** *(minimal changes on the foveal edge of the scar)*.
On TD-OCT, the scar is hyper-reflective. Note at the foveal edge of the scar, a minimal elevation of the RPE due to recurrence, combined with an adjacent SRD.

***Spectralis** horizontal section, associated with fluorescein angiography.**
SD-OCT shows a dense hyper-reflective scar with back-shadowing. The recurrence and the PED are adjacent to the scar, with an accentuation of the SRD. Note the bright hyper-reflective spots and the moderate intraretinal fluid accumulation.

RECURRENCE AND SRD

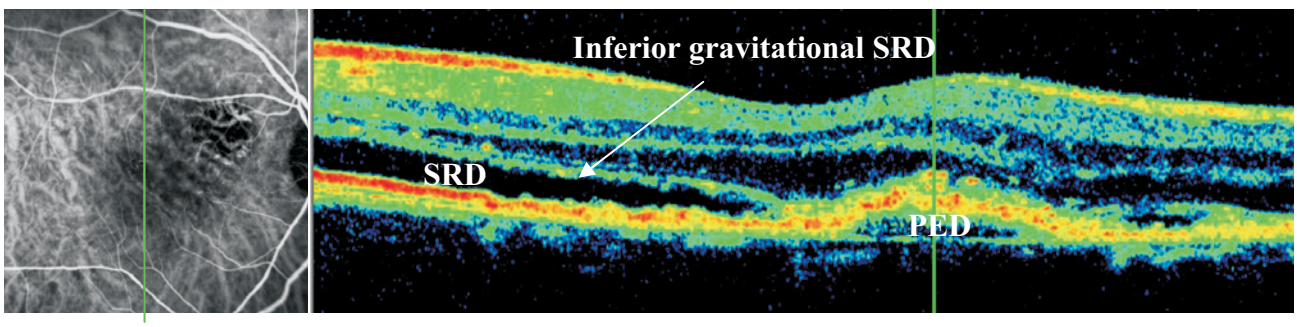


Figure 55: Fluid accumulation, anterior to the RPE and predominantly downward shifting.

***Spectralis** horizontal section, associated with ICG angiography** *(supero- nasal post-laser scar associated with an occult subfoveal recurrence with PED and shifting SRD)*.

On SD-OCT, the inferior SRD is accentuated and visible in the inferior part of the vascularized PED.
Note several bright spots and intraretinal fluid but still good organization of the retinal layers. VA: 20/40.

SRD and RPE TEAR

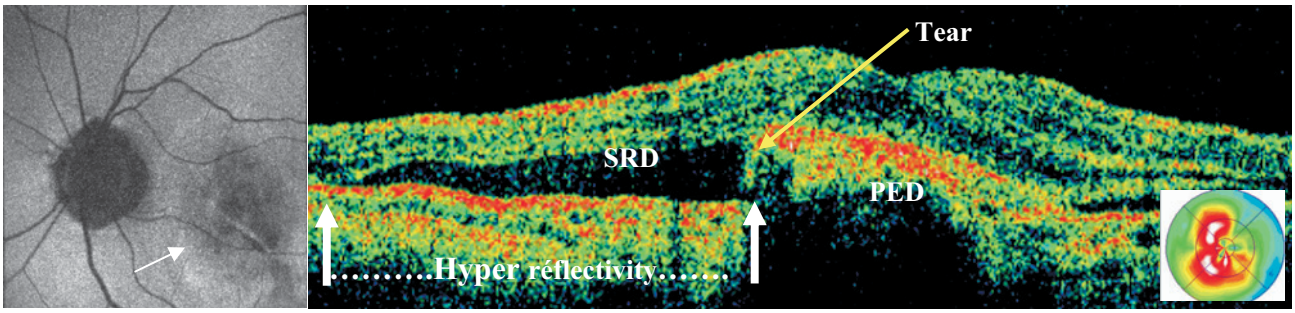


Figure 56: Fluid accumulation, anterior to the RPE, over a recent tear of the RPE.

a): Autofluorescence: Note the inferonasal RPE-tear and adjacent exudative reaction (*arrow*).

b): *Stratus horizontal section.**
On **TD-OCT**, extensive SRD over all of the choroidal zone exposed by the RPE tear and retraction.

Note the hyper-reflectivity in this zone, which extends far posteriorly towards the choroid.
In the superior half of the lesion, the PED persists with partial organization of the retracted fibrovascular tissue.

SRD and RETINAL HEMORRHAGE

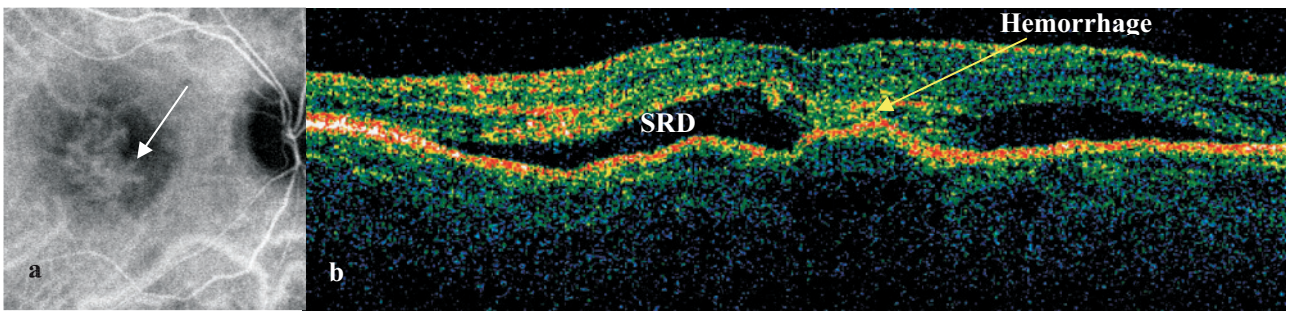


Figure 57: Fluid accumulation, anterior to the RPE, indicating an active phase of occult choroidal neovascularization with retinal hemorrhage.

a): ICG angiography: demonstration of the CNV network and hemorrhage (*arrow*).

b): *Stratus horizontal section.**
On **TD-OCT**, the SRD involves the entire surface of the vascularized PED and extends slightly beyond.

Note the zone of hyper-reflectivity corresponding to deep retinal hemorrhage, very close to the center.

3. Fluid Accumulation Anterior to the RPE

Cystoid Macular Edema

Cystoid macular edema, the second type of retinal alteration related to abnormal leakage, is accumulation of serous (or predominantly serous) fluid within the neurosensory retina. It may consist of:

- Diffuse intraretinal fluid, or
- Intraretinal cysts.

Simple intraretinal fluid **infiltration** is a common feature and is easy to measure, as it causes increased retinal thickness, which is particularly important in the central foveal or foveolar region.

This increased central retinal thickness (CRT) in the central 1000 µm of the fovea can be **measured automatically** and rapidly by OCT software. It can also be corrected manually to avoid well known sources of error (**Figure 58**).

All OCT systems are equipped with more or less similar complex **measuring devices**. With SD-OCT, retinal thickness measurements are displayed on numerical representations, false-color scales, and/or map representations (**Figure 60**).

Different images and/or measurements or graph **overlay processes** can be used to follow and analyze the response to treatment. This has been further improved by precise ***eye-tracking*** systems, allowing measurements to be automatically repeated in exactly the same place.

3D images can also be used to easily detect and study the different areas of the macula and to avoid overlooking a slightly eccentric or small lesion.

Intraretinal cystic spaces, suggesting the histological appearance of cystoid macular edema, may be observed at different stages of the disease:

- **Isolated** or **associated** with diffuse intraretinal fluid and/or SRD (**Figures 58-60**),
- **Small** or **large** and/or sometimes very extensive (**Figures 61-63**),
- **Single** or **multiple** (**Figure 64**).

Intraretinal cysts are usually situated in the central macula and the foveal avascular zone, where they often become confluent; they are always larger than more peripheral cysts (**Figures 65 and 66**).

These cystoid spaces can be tightly packed or scattered. They may be organized in one or two layers, with a predilection for the plexiform layers (**Figures 67-69**).

Intraretinal cystoid spaces almost always reflect marked exudation from choroidal neovascularization. They can resolve in response to treatment, often more rapidly than the SRD.

They can also be associated with more chronic, older lesions with marked fibrosis (**Figures 70-72**).

Later in the course, intraretinal cysts can be a sign of **irreversible degeneration** of the neurosensory retina and persist even after resolution of leakage. In these cases, the diagnosis is based on the hyper-reflective zone of fibrosis and the absence of SRD (as well as marked loss of visual acuity).

Intraretinal cysts and diffuse intraretinal fluid are therefore easy to recognize on OCT images and constitute a major sign to be detected and quantified in wet AMD.

These cystoid spaces are rarely isolated. Indirect signs of CNV proliferation are always present, either as a preretinal zone of hyper-reflectivity corresponding to classic CNV or as a vascularized PED, which is always associated with occult CNV.

SD-OCT more precisely visualizes and allows follow-up of associated signs such as bright hyper-reflective spots and intraretinal dense zones, which are probably signs of associated inflammatory response and worsening of the lesions.

DIFFUSE INTRARETINAL FLUID

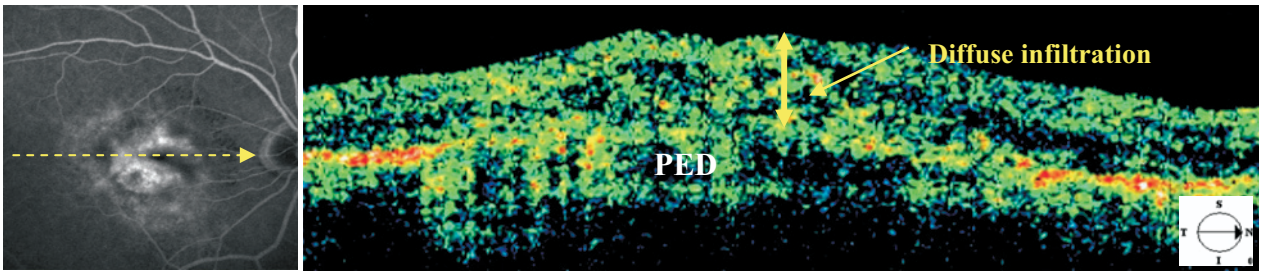
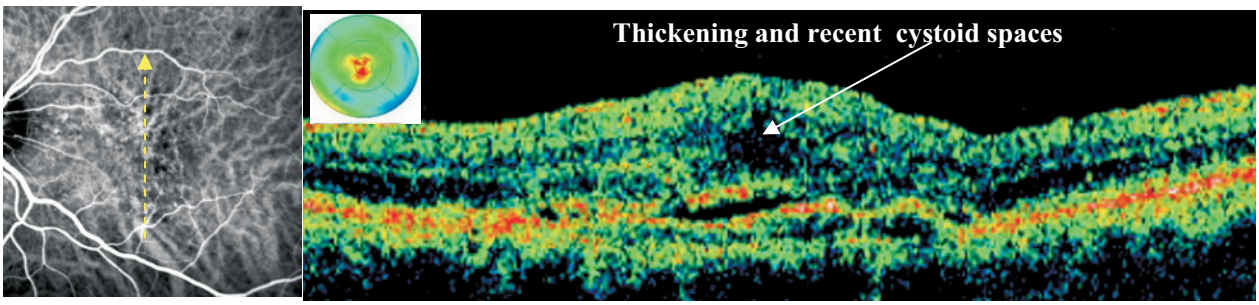


Figure 58: Diffuse intraretinal fluid and thickening of the macular neurosensory retina.
***Stratus** horizontal section, associated with fluorescein angiography (*leakage and edema*).**
On **TD-OCT**, diffuse intraretinal fluid accumulation induces thickening with flattening of the foveal depression. Retinal layers are disorganized anterior to the RPE. The RPE band is poorly visible. Presence of an old PED.



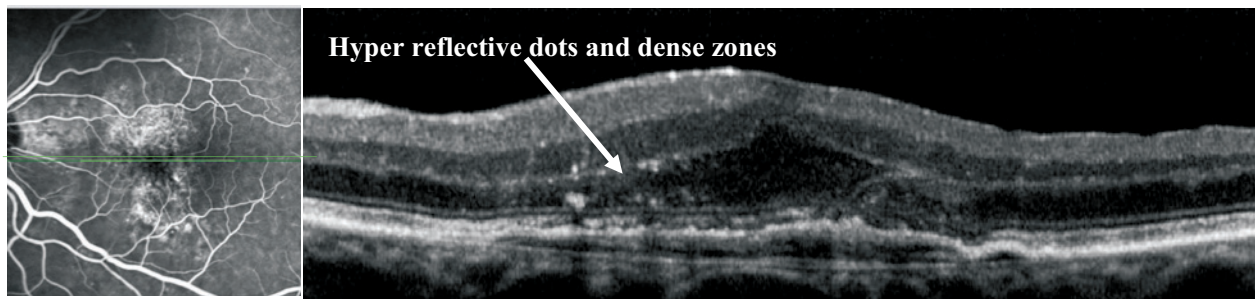


Figure 59: Fluid accumulation anterior to the RPE: diffuse intraretinal fluid, thickening of the macular neurosensory retina and intraretinal cyst.
***Stratus** vertical section associated with ICG angiography demonstrating the occult CNV network.**
On TD-OCT, the retina is thickened with flattening of the foveal depression. Retinal layers are disorganized in the center and replaced by a poorly-delineated cystoid space.
***Spectralis** horizontal section associated with fluorescein angiography.**
The retinal structure is more precisely visualized on SD-OCT: alterations of the outer layers and bright hyper-reflective spots around the cystoid spaces in the outer nuclear layer. Note the dense zones anterior to the external limiting membrane.

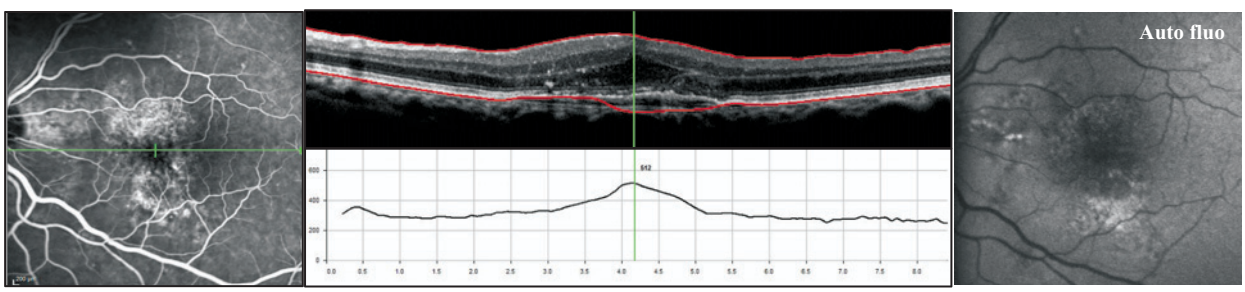


Figure 60: Fluid accumulation anterior to the RPE. Graphic representation of retinal thickness measurements (between the 2 red lines) as far as Bruch's membrane.

CYSTOID SPACES

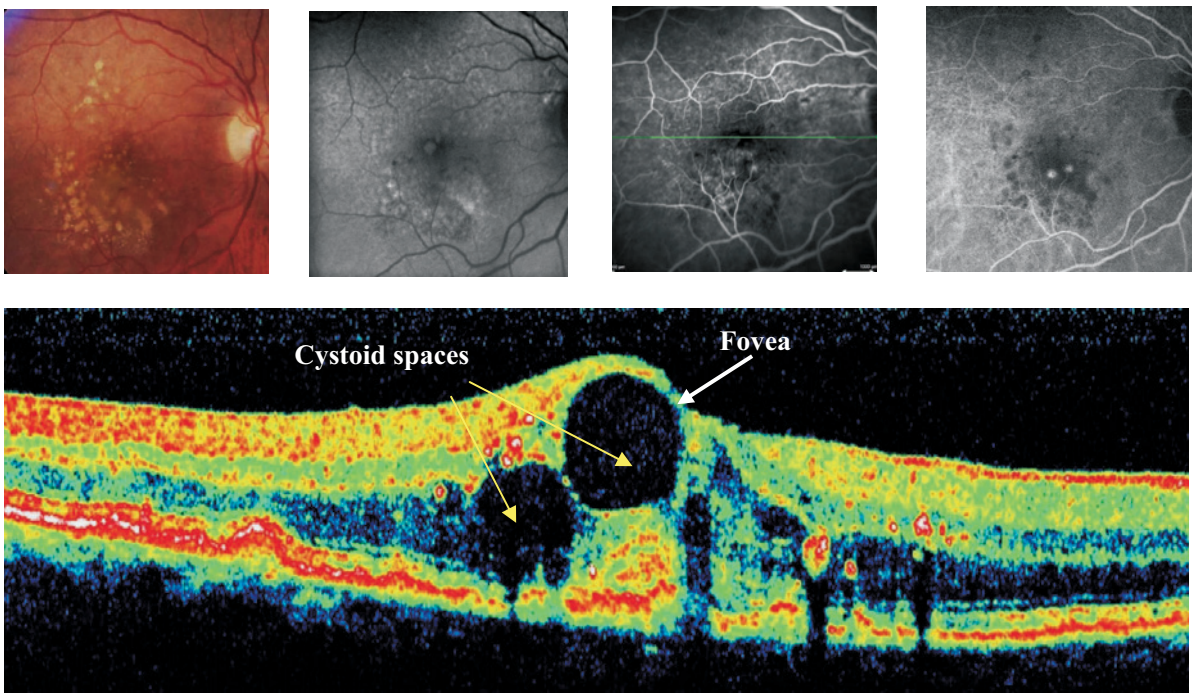


Figure 61: Fluid accumulation anterior to the RPE: two predominant cystoid spaces **in the central area.**
***Spectralis** horizontal section, associated with fluorescein angiography** *(juxtafoveal leakage).*
On SD-OCT, the retina is raised by a large, almost central well-delineated cyst. Note a second, deeper paracentral cyst.
VA: 20/100.

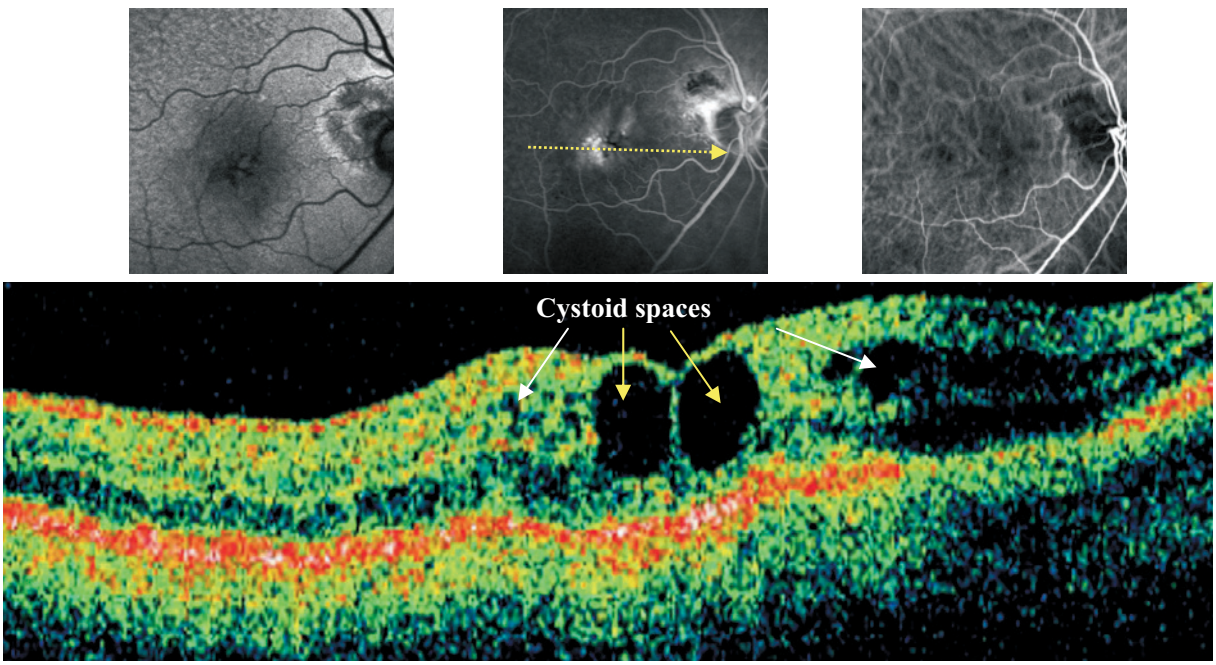


Figure 62: Fluid accumulation anterior to the RPE: two predominant cysts in the central area.
***Stratus** horizontal section shown with fluorescein angiography**: foveal leakage.
On TD-OCT, the retina shows thickening, the foveal depression is raised by two large and very well-delineated central cysts just underneath the inner limiting membrane. Note the presence of several adjacent cysts, much smaller and closely packed. VA: 20/50.

CYSTOID SPACES

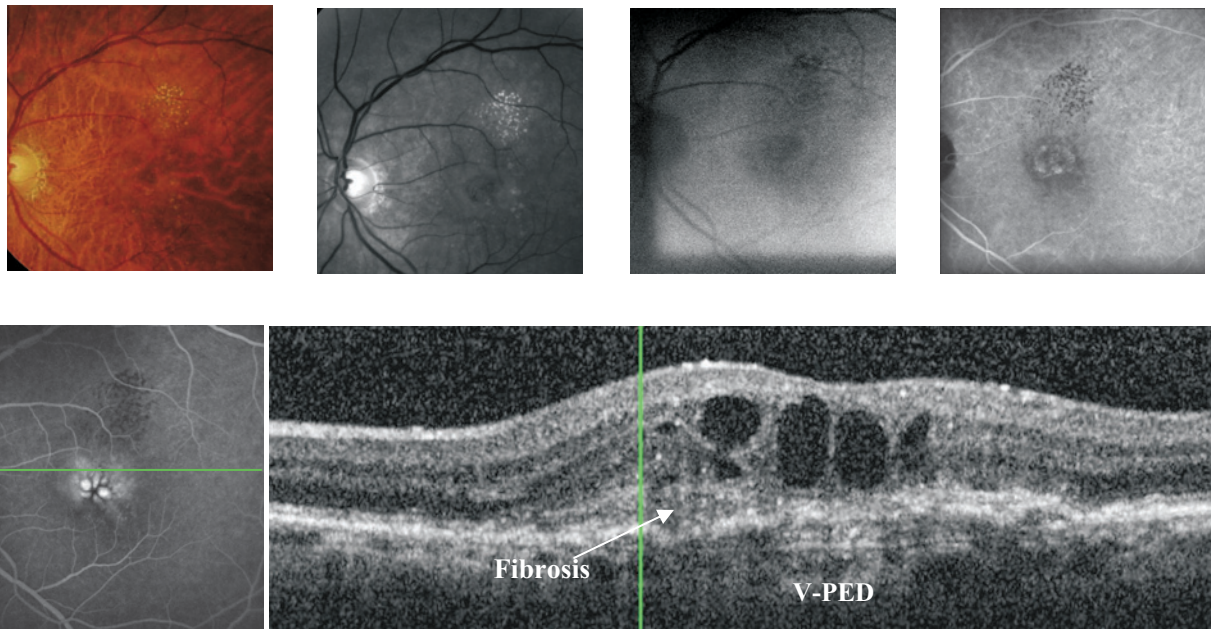


Figure 63: Fluid accumulation anterior to the RPE: old isolated cysts.
***Spectralis** horizontal section associated with fluorescein angiography** (*cystoid macular edema*).
On SD-OCT, the central retina is thickened by large, well-delineated cystoid spaces underneath the inner limiting membrane. Note the absence of SRD. Early signs of fibrosis anterior to the organized vascularized PED are suggestive of an old lesion. VA: 20/80.

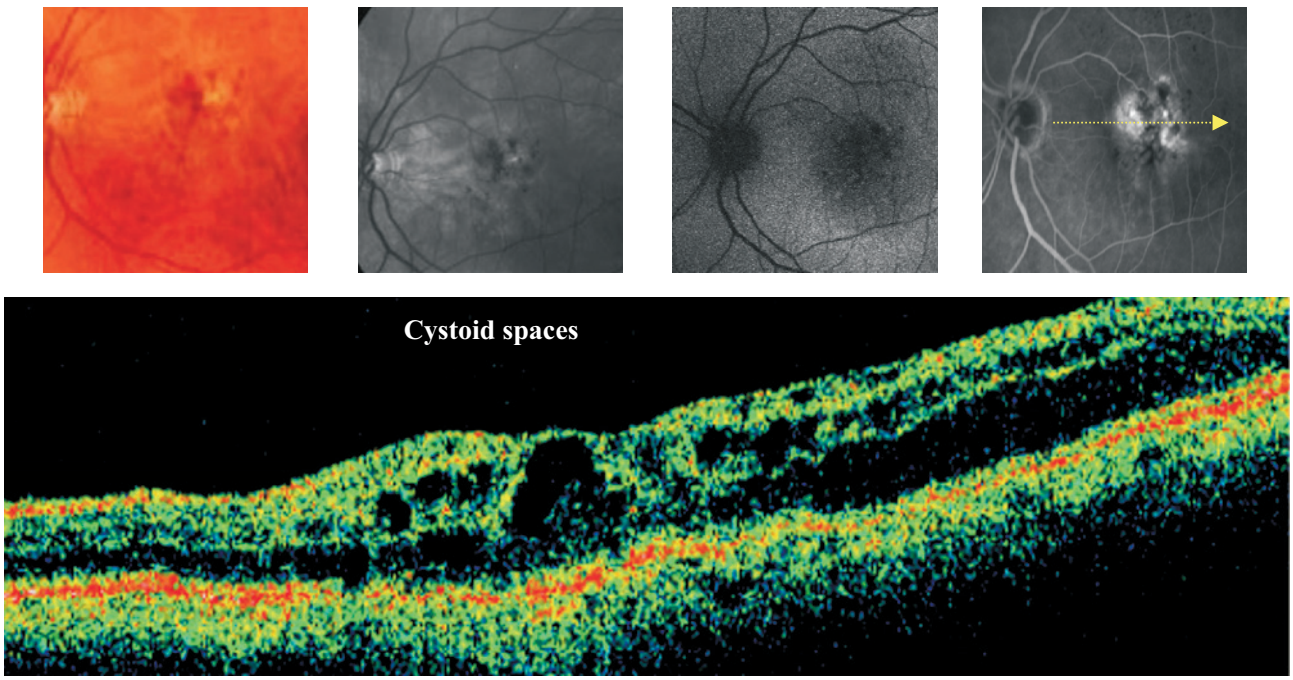
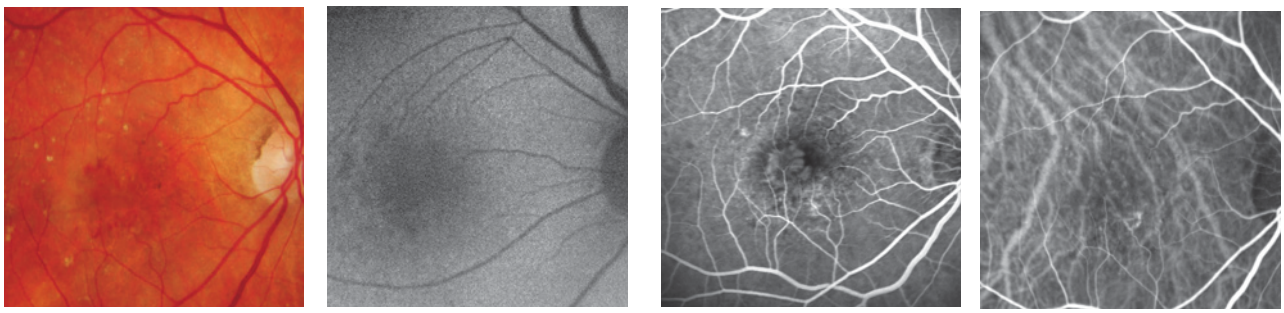
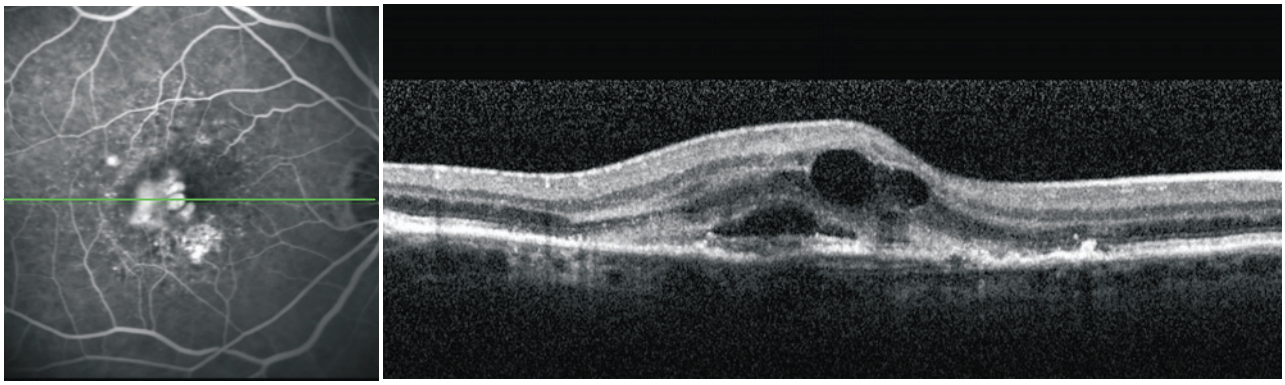


Figure 64: Fluid accumulation anterior to the RPE: large number of multiple cysts. VA: 20/63.
***Stratus** horizontal section associated with fluorescein angiography** *(advanced chorioretinal anastomosis).*
On TD-OCT, the central retina is thickened by many well-delineated cysts, confluent in the center and associated with diffuse intraretinal fluid accumulation (anterior to a vascularized PED, which is flat on this section).

CYSTOID SPACES





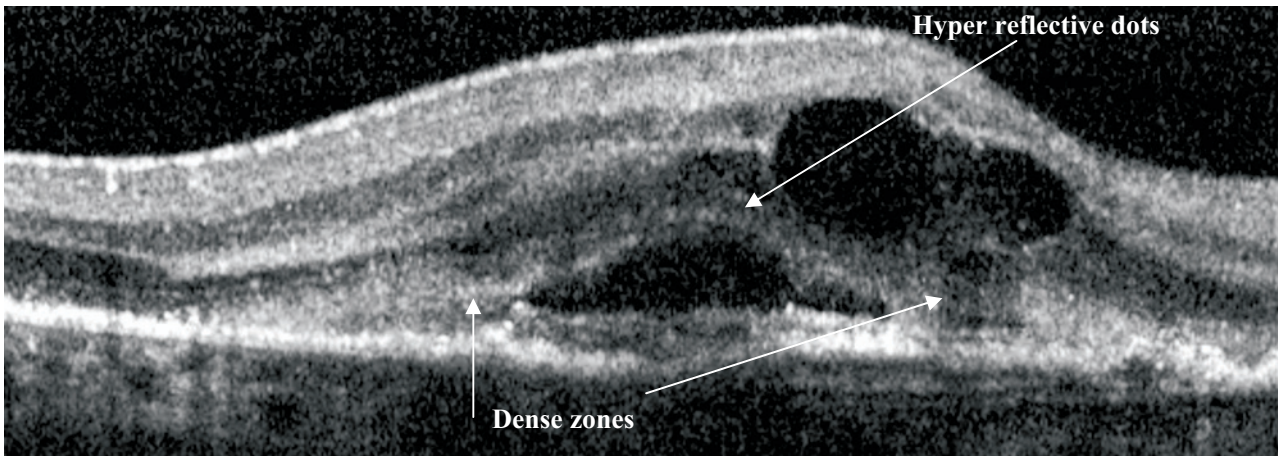


Figure 65: Fluid accumulation anterior to the RPE: large central cysts.

***Spectralis** horizontal section associated with fluorescein angiography** (*mixed CNV*).

On SD-OCT, the enlarged view shows the various tissue changes.

Note the scattered bright hyper-reflective spots predominantly in outer layers and around the cysts. Zones of intraretinal densification are visible at the level of the outer nuclear layer and the external limiting membrane. These layers remain visible in all regions, while the IS/OS interface is severely altered. VA: 20/50.

CYSTOID SPACES

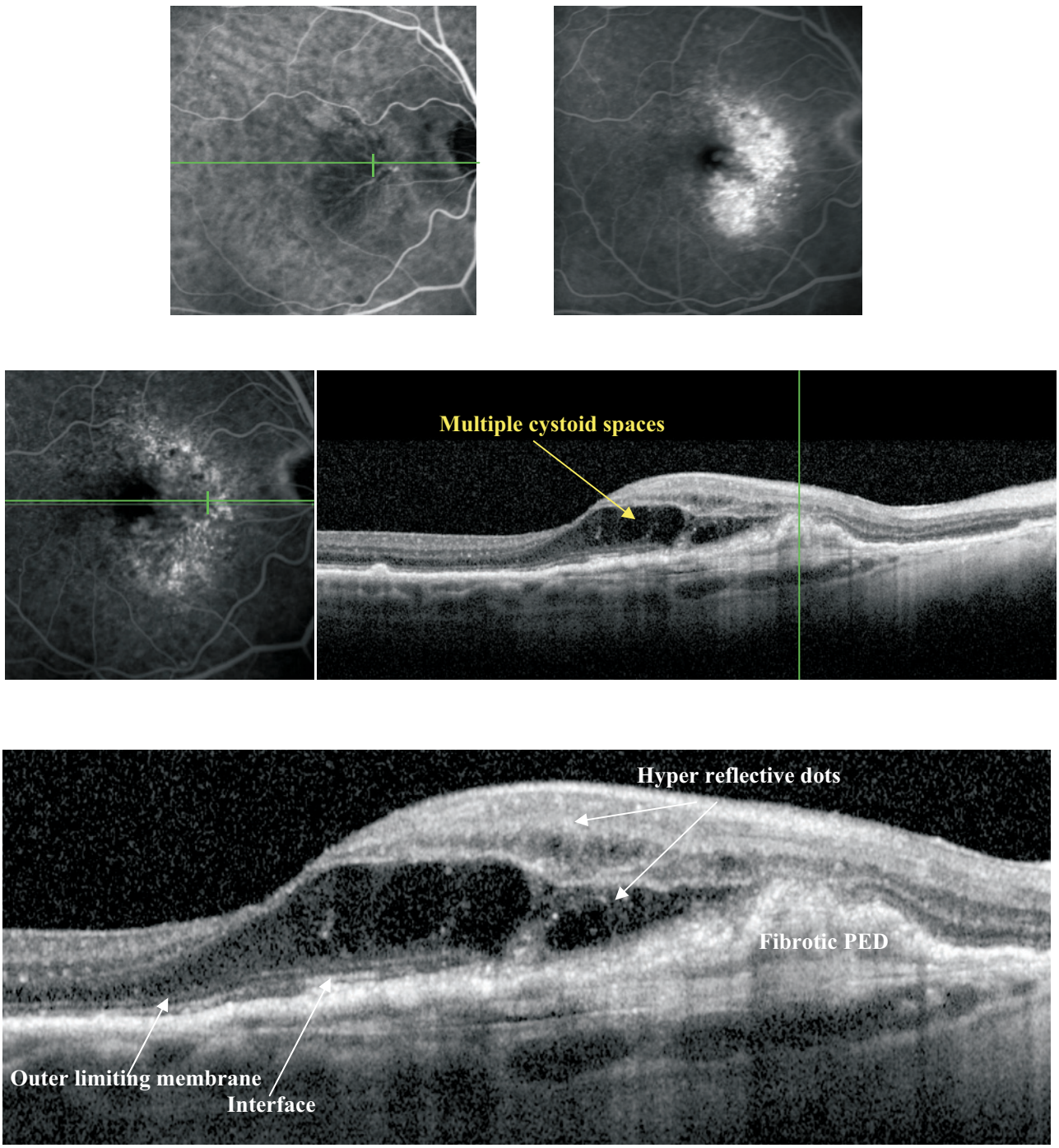


Figure 66 Fluid accumulation anterior to the RPE: large central cysts.

***Spectralis** horizontal section associated with angiography** *(advanced occult CNV).*

On SD-OCT, the enlarged view shows the limits of the cysts delineated by bright hyper-reflective spots, predominantly in the outer layers. Note that the outer nuclear layer, external limiting membrane, and IS/OS interface remain visible, except over the area of occult CNV (indicated by the calliper on the green line). The PED is fibrotic and hyper-reflective. VA: 20/50.

MULTIPLE CYSTS IN SEVERAL LAYERS

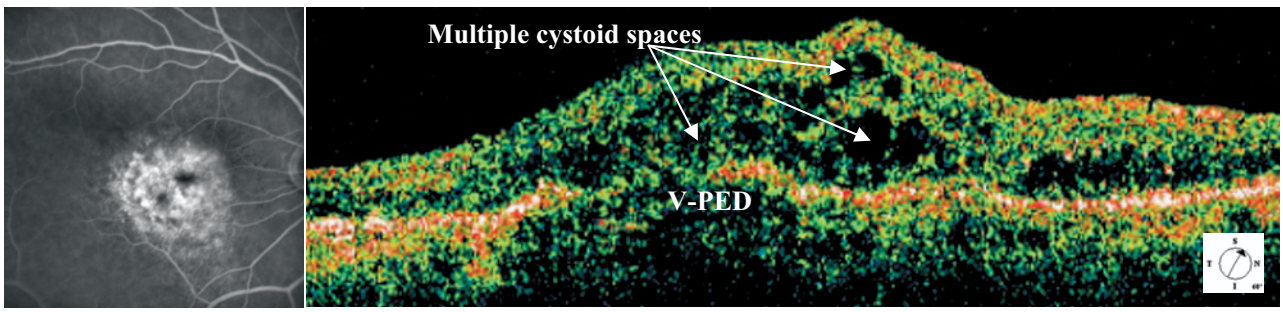


Figure 67: Fluid accumulation anterior to the RPE: multiple central cysts in several layers.
***Stratus** horizontal section associated with angiography** (*occult CNV and advanced multiple anastomosis*).
On TD-OCT, the retina is considerably thickened and infiltrated with multiple large cysts, often confluent and sometimes involving several layers.
Note the old, partially-organized, vascularized PED with a break or disruption of the RPE band.

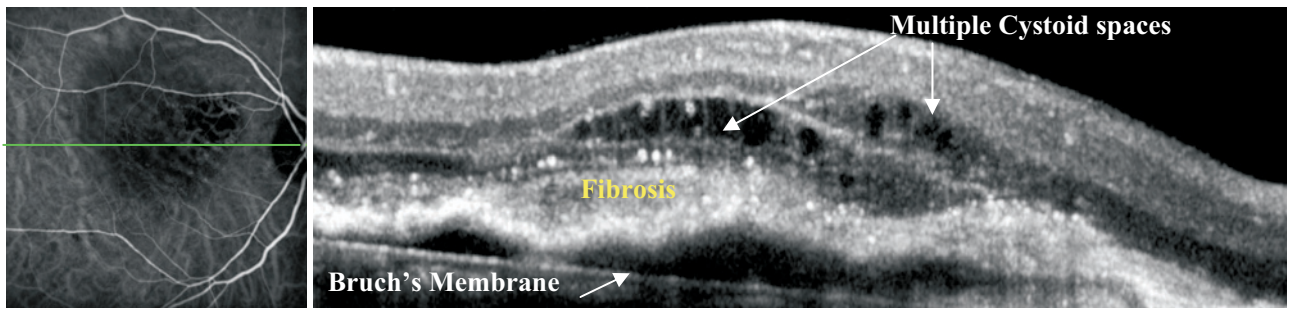


Figure 68: Fluid accumulation anterior to the RPE: multiple central cysts in several layers.
***Spectralis** horizontal section associated with ICG angiography** *(dark persistent PED but poorly perfused, barely visible network).*
On SD-OCT, persistence of multiple, small cysts in the outer layers, despite treatment. These cysts are associated with the persistence of many bright spots and the development of dense, hyper-reflective material anterior to the RPE. The wavy, multilobed, vascularized PED is still visible but is fairly flat.

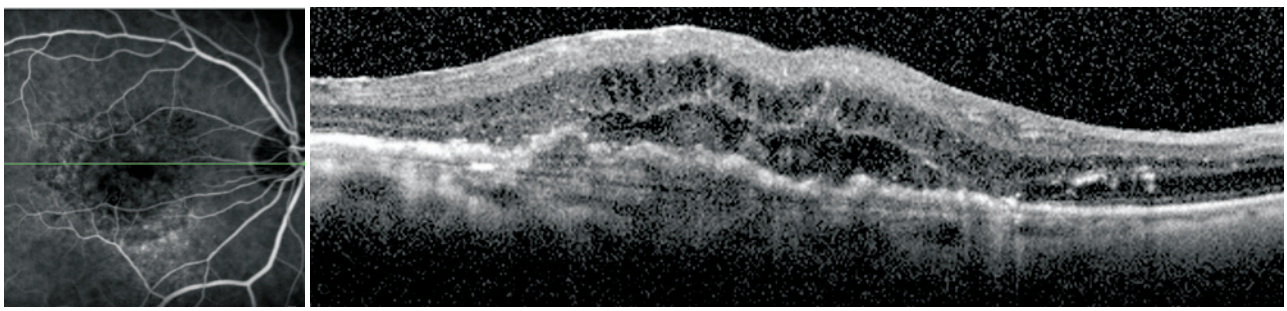


Figure 69: Fluid accumulation anterior to the RPE: large number of small cysts.
***Spectralis** horizontal section associated with fluorescein angiography** *(partial regression of CNV*).
On SD-OCT, persistence of marked intraretinal fluid accumulation with a large number of cysts in the outer plexiform layer. The outer nuclear layer is modified with a number of bright hyper-reflective spots and partial densification, which persists even after many treatment sessions.
These alterations and cysts are situated anterior to a persistent PED, which has become partially organized despite treatment.
No improvement of visual acuity. VA: 20/800.

RESIDUAL CYSTS AFTER TREATMENT

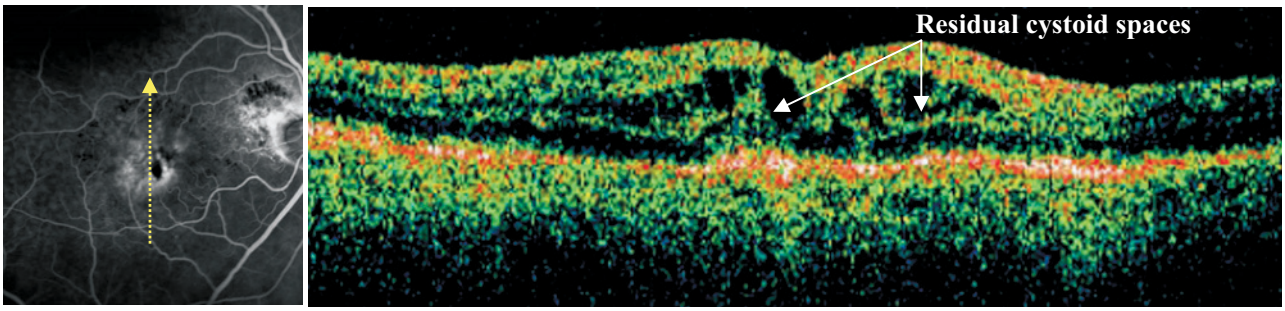


Figure 70: Fluid accumulation anterior to the RPE: large number of small cysts.
***Stratus** vertical section associated with fluorescein angiography** *(partial regression of CNV)*. VA: 20/50.
On TD-OCT, the intraretinal cysts, particularly marked in this case of chorioretinal anastomosis, have only partially regressed and persist with diffuse intraretinal fluid and moderately increased retinal thickness.

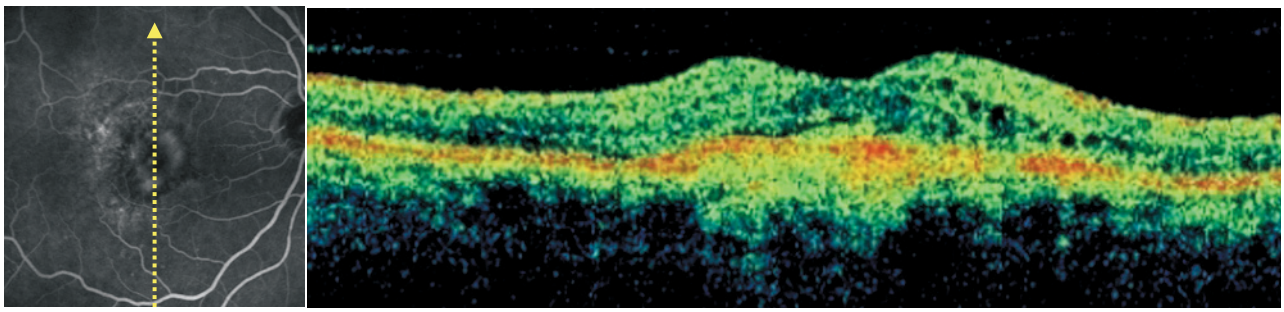


Figure 71: Fluid accumulation anterior to the RPE: multiple small persistent cysts.
***Stratus** vertical section associated with fluorescein angiography** *(partial regression of CNV)*. VA: 20/63.
On TD-OCT, the foveal depression is normalized, suggestive of a good visual prognosis. A moderate thickening of the retina persists with a series of small cysts in the outer plexiform layer, especially in the superior macular region but sparing the center.
Progressive healing of the neovascular membrane with moderate fibrosis.

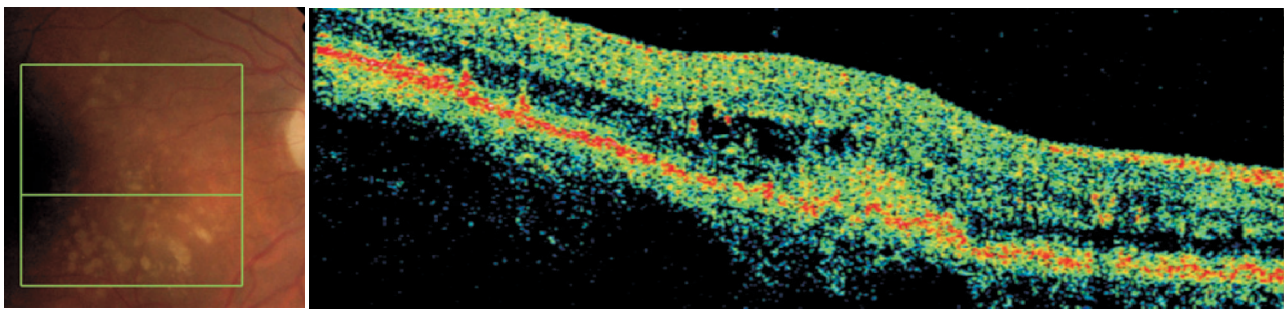


Figure 72: Fluid accumulation anterior to the RPE: persistence of several cysts in front of a moderate fibrosis.
***Topcon** horizontal section associated with a color photograph.** Morphological and functional stabilization.
On SD-OCT, regression of exudative signs is accompanied by reapplication of the retina, which remains moderately thickened. Several cysts are still visible adjacent to the small fibrotic scar. VA: 20/160.

Study on the Characteristics of Intraretinal Cysts in AMD

A consecutive series of 150 patients with wet AMD was analyzed in an independent and blinded study to compare fluorescein angiography, SLO-ICG angiography, and OCT.

This study was designed to objectively determine the value of these various imaging modalities (fluorescein angiography, SLO-ICG angiography, and OCT), alone or in combination, for diagnosis, and to guide treatment.

In this context, OCT examinations demonstrated the presence of intraretinal cysts in almost one half of patients (62 patients, 41%).

In this group of 62 patients, cysts were almost always multiple (97%) and were isolated or central in only 2 patients (3%).

Cysts were associated with the presence of diffuse intraretinal fluid with a significant increase of retinal thickness (more than 50 µm or more than 25%) in 36 patients (58%).

The **presence of subretinal fluid** with serous retinal detachment (SRD) was detected in more than one-third of patients (24 patients, 39%).

The **dimensions** of intraretinal cysts varied according to the stage and history of the lesions.

- Small cysts in 70% of cases,
- Large or confluent cysts in 30% of cases.

The **extent** of the cysts also varied according to the history of the lesions:

- Visible in only one layer in 42% of cases,
- Visible in two layers in 58% of cases.

In longstanding, advanced forms associated with varying degrees of **fibrosis**, cysts remained visible in 20 patients (30%), which corresponded to irreversible degenerative lesions with severe loss of visual acuity.

Cysts were usually accompanied by probable **inflammatory response** (bright hyper-reflective spots and dense zones) that showed a similar response to treatment (regression or recurrence).

These reactive signs were accompanied by **disorganization** of the retinal layers.

Bright hyper-reflective spots were clearly visible in most cases (70%).

During treatment, after 3 intravitreous injections of anti-VEGF, cysts were still present in 22 of the 62 patients (35%).

Resolution of cysts appeared to be delayed compared to functional improvement.

Conclusion

The course of intraretinal cysts and intraretinal fluid may follow that of the other signs of AMD, or may be delayed, or they may persist despite resolution of other signs.

The most difficult problem is to distinguish a *residual lesion* that is likely to resolve from persistent cysts reflecting irreversible alteration of the retina.

Other functional studies and imaging modalities are particularly valuable in this setting.

IV. Anterior to the RPE Band: Bright Hyper-reflective Spots and Dense Zones

The combined presence of these signs (bright hyper-reflective spots and intraretinal dense zones) is detected only rarely on TD-OCT.

They are clearly visible and more easily analyzed on Spectral-Domain OCT, especially with the *Spectralis**.

- The presence and integrity of the **external limiting membrane** and **IS/OS interface** must be confirmed.

These relatively dense lines can be altered, disrupted, or on the contrary, thickened over AMD lesions (**Figure 73**).

The external limiting membrane and IS/OS interface constitute landmarks to evaluate the inner and outer segments, which corresponds to hypo-reflective bands situated between these two lines.

- Modifications of the IS/OS interface are particularly marked over active CNV, either classic or occult.

These changes usually resolve in response to treatment, especially when treatment is started early in the course of the disease (**Figures 74 and 75**).

These signs therefore have a prognostic value and should be analyzed and compared on follow-up examinations, in the same way as intraretinal fluid and cysts.

Bright Hyper-reflective Spots

Bright hyper-reflective spots often appear to accumulate on the inner and outer limits of the SRF or cysts (**Figure 76**).

They can also be more disseminated, involving even the innermost layers.

They usually resolve gradually in response to treatment (**Figures 77 and 78**) and can therefore constitute markers of neovascular lesion activity.

Hyper-reflective Material

This relatively dense material probably reflects an inflammatory reaction. It appears to accumulate in the space situated between the external limiting membrane and the IS/OS interface. It also appears to be an important marker related to deterioration of the lesions (**Figure 79**).

Response to Treatment

In most cases, the efficacy of treatment is largely evaluated in terms of regression of intraretinal fluid and reattachment of the retina.

In parallel, bright hyper-reflective spots and dense material appear to be reliable markers of the activity of the lesions. Their resolution usually indicates a good response to treatment (**Figures 79 and 80**). In contrast, these signs persist and deteriorate in the case of progressive fibrosis (**Figure 81**).

In a series of 30 patients with active occult CNV initially examined by SD-OCT and then reassessed monthly, all patients presented bright hyper-reflective spots and major alterations of the outer nuclear layer and IS/OS interface.

After 3 IVT sessions, bright hyper-reflective spots resolved in parallel with improvement of VA in 20 patients (66%).

In another 8 patients, bright hyper-reflective spots decreased but in the context of progressive fibrosis with loss of visual acuity, and 2 patients had persistent cystoid degeneration.

These alterations of the external limiting membrane, IS/OS interface, and RPE, and the presence and course of bright hyper-reflective spots and dense zones in the outer nuclear layer can provide useful information to evaluate the presence and degree of photoreceptor damage.

EXTERNAL LIMITING MEMBRANE, IS/OS INTERFACE, RPE

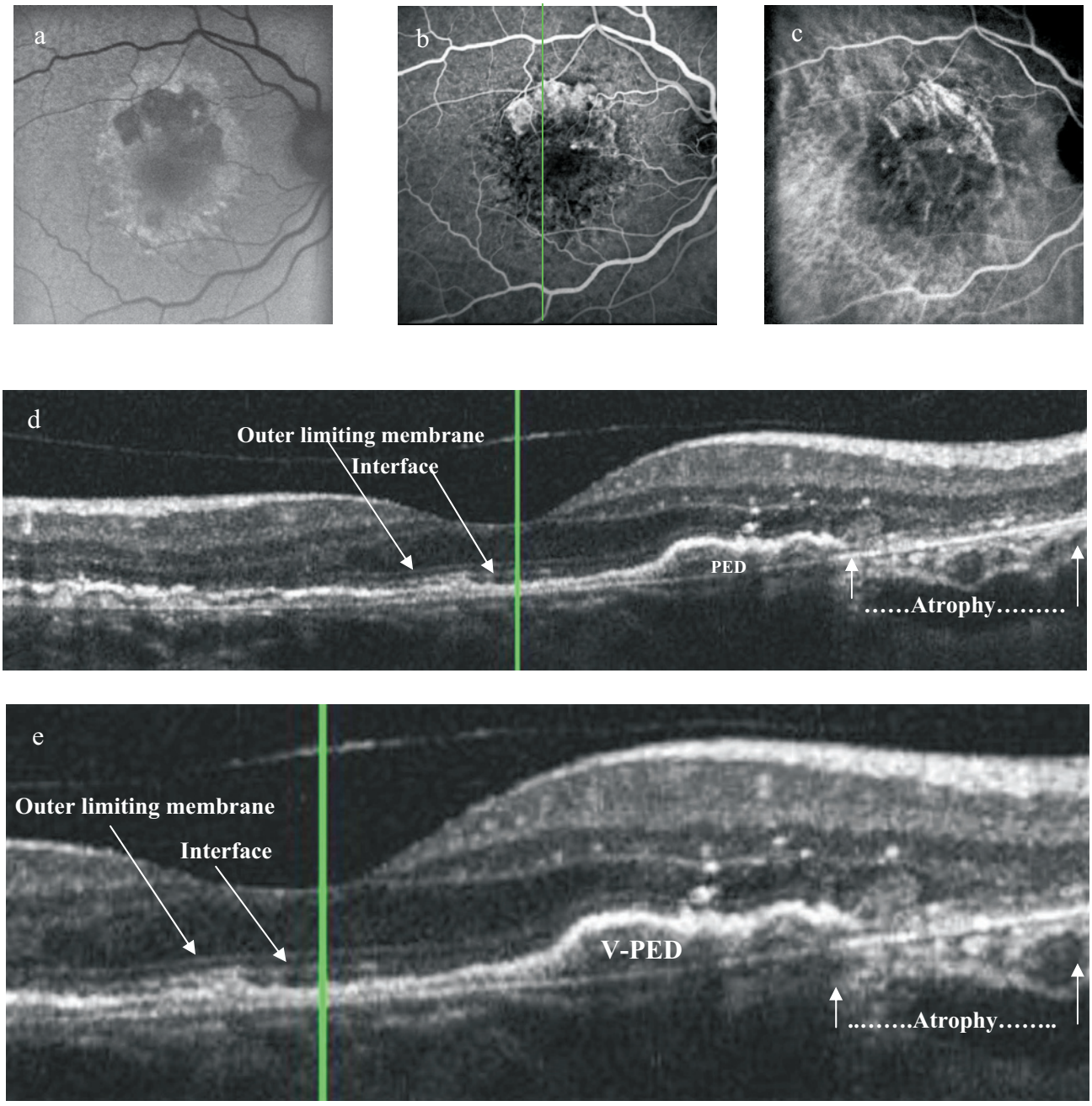


Figure 73: External limiting membrane and IS/OS interface.
a, b, and c): Autofluorescence, fluorescein angiography, and ICG angiography: complex lesion with occult CNV and atrophic areas in the superior part of the macula.
d): *Spectralis SD-OCT horizontal section**.
In the inferior macular region: flat PED; Bruch's membrane is visible, distinct from the irregular and thickened RPE, the IS/OS interface is intermittent, and the external limiting membrane is poorly visible.
In the central foveal zone, the three bands are clearly visible and only slightly altered: visual acuity is maintained at 20/32.
e): Enlarged view: in the superior macular region, over the vascularized PED: the external limiting membrane and IS/OS interface are no longer visible and numerous *bright hyper-reflective spots* can be seen.
In the superior atrophic zone, the RPE, IS/OS interface, external limiting membrane, and even the outer nuclear layer have disappeared.

EXTERNAL LIMITING MEMBRANE, IS/OS INTERFACE, RPE

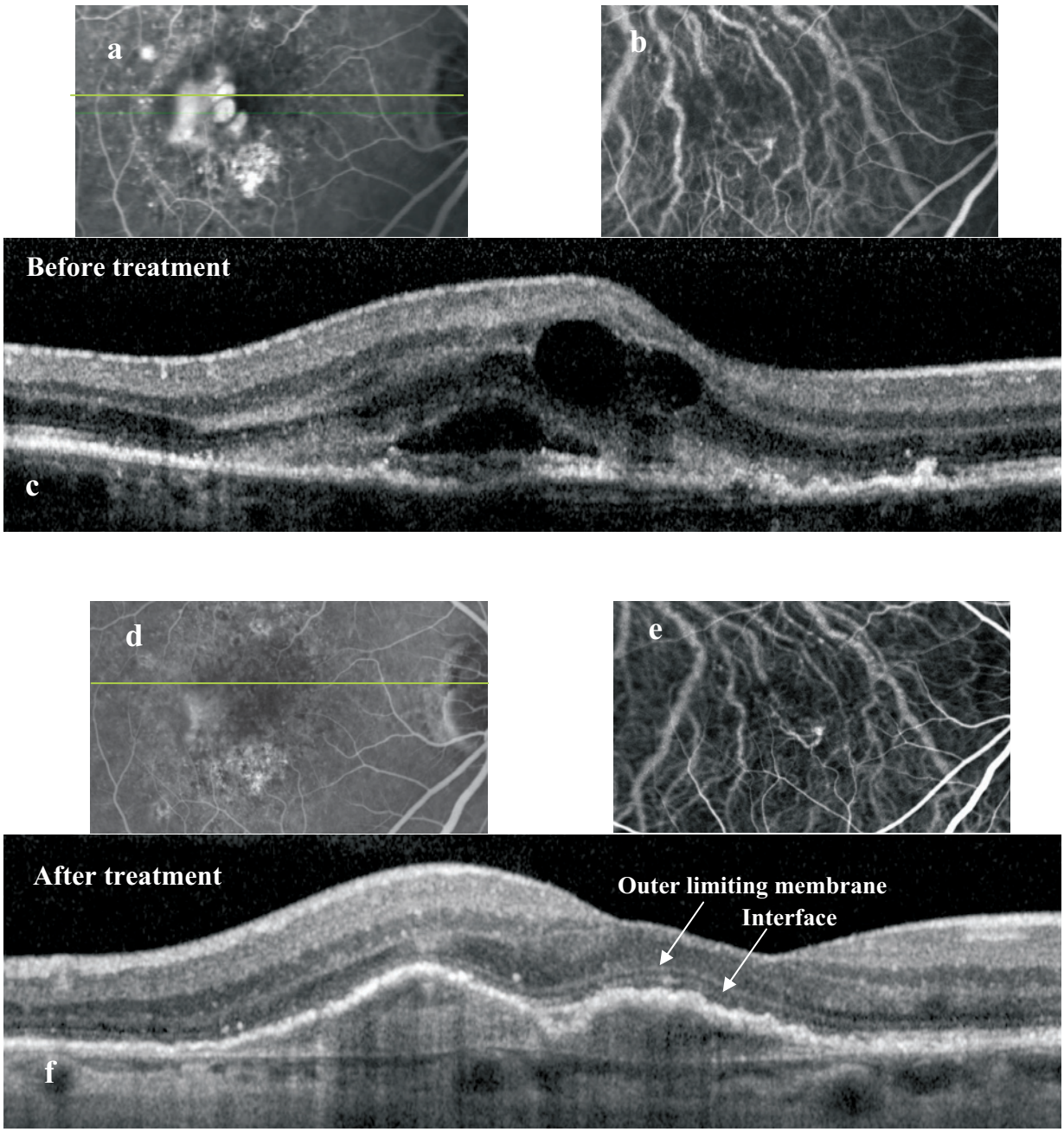


Figure 74: External limiting membrane and IS/OS interface.
a, b, and c): Before treatment:
***Spectralis** horizontal section correlated with fluorescein angiography and ICG angiography** *(mixed lesion with occult and classic CNV and marked cystoid spaces)*.
SD-OCT: in the foveal zone, very large cysts with major changes of the three bands and outer nuclear layer invaded by a dense zone and bright hyper-reflective spots. VA: 20/50.
d, e, and f): After treatment:
***Spectralis** horizontal section**: reattachment and decreased thickness of the retina and almost normal appearance of the external limiting membrane, IS/OS interface, and outer nuclear layer. VA: 20/32.

EXTERNAL LIMITING MEMBRANE, IS/OS INTERFACE, RPE

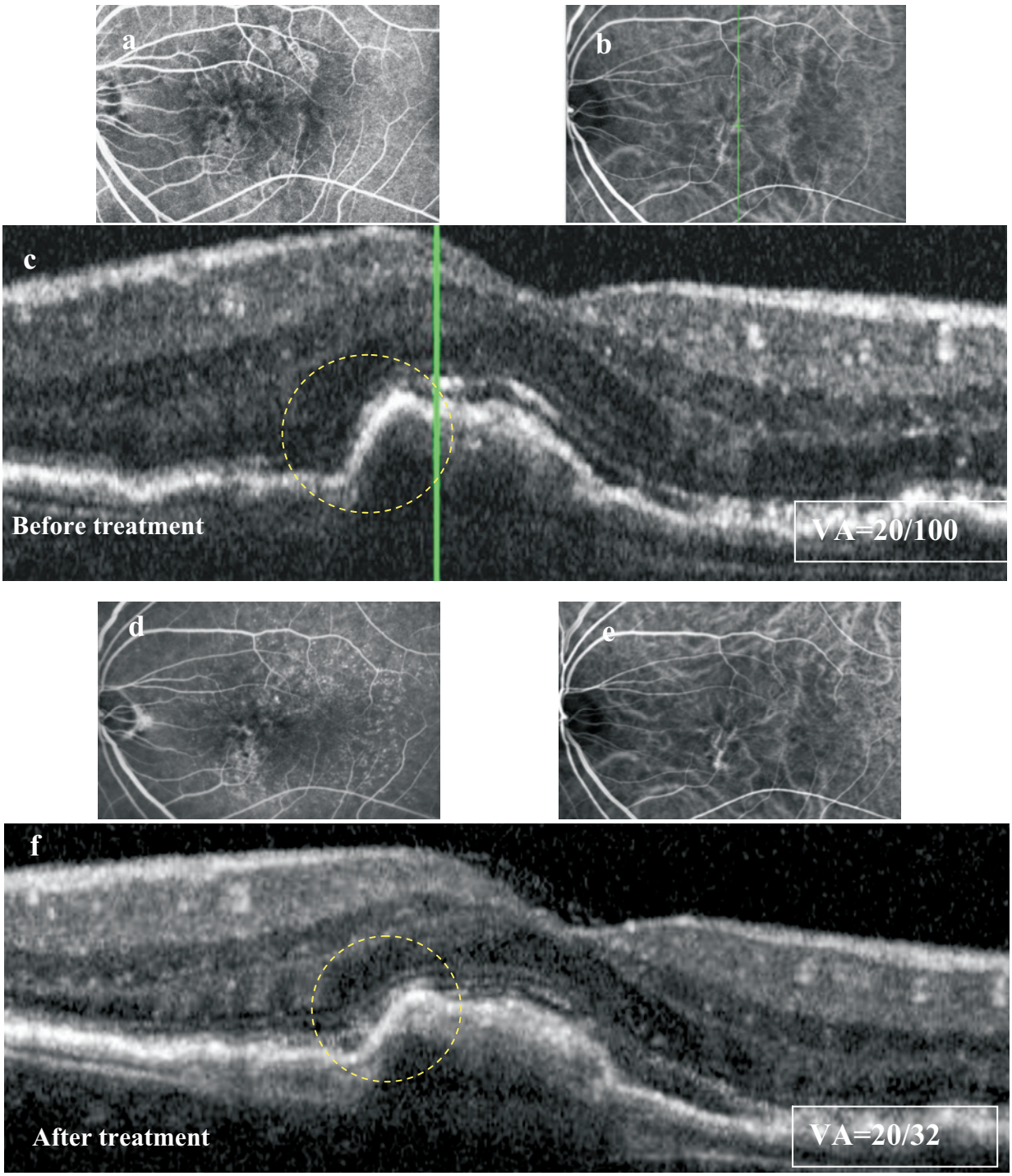


Figure 75: External limiting membrane and IS/OS interface.

a, b, and c): Before treatment. VA: 20/100.
***Spectralis** horizontal sections**: occult CNV and vascularized PED.
SD-OCT: in the foveal zone, irregularities and alterations of the three bands and disruption of the IS/OS interface (*circle*).
d, e, and f): After treatment, VA: 20/32.
After an injection of anti-VEGF, decreased thickness and almost normal appearance of the external limiting membrane, IS/OS interface, and outer nuclear layer (*circle*).

EXTERNAL LIMITING MEMBRANE, IS/OS INTERFACE, RPE

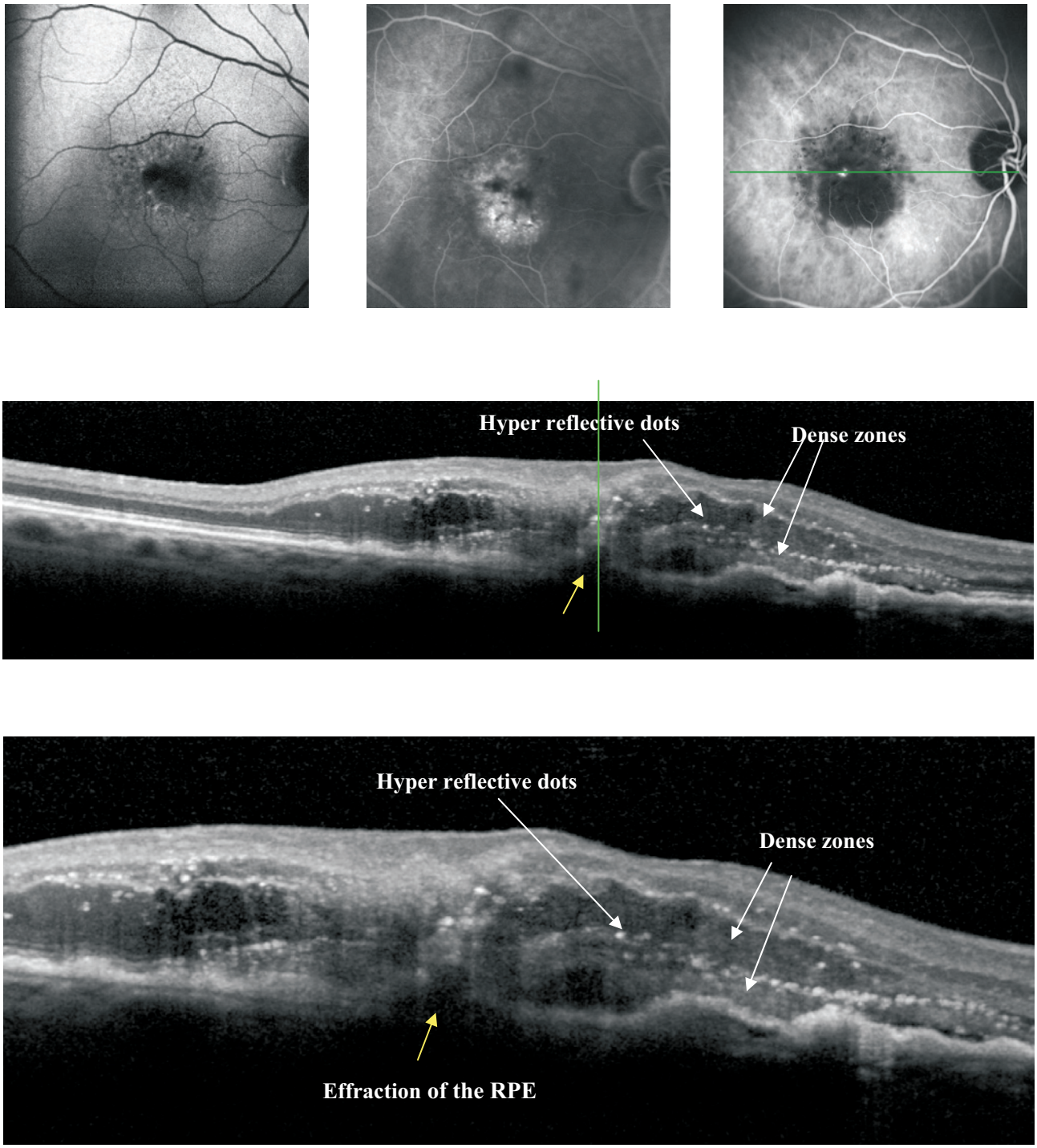


Figure 76: Hyper-reflective spots and dense zones.

Autofluorescence, fluorescein angiography, and ICG angiography: vascularized PED and probable chorioretinal anastomosis.
***Spectralis** horizontal section:**
SD-OCT: retina detached and thickened by numerous cysts in the foveal zone with numerous bright hyper-reflective spots highlighting the limits of the cysts, the IS/OS interface, and external limiting membrane (which are poorly visible). Large dense zone in the outer nuclear layer.
Note the break of the RPE at the site of the anastomosis (*yellow arrow*). VA: 20/80.

BRIGHT HYPER-REFLECTIVE SPOTS AND DENSE ZONES

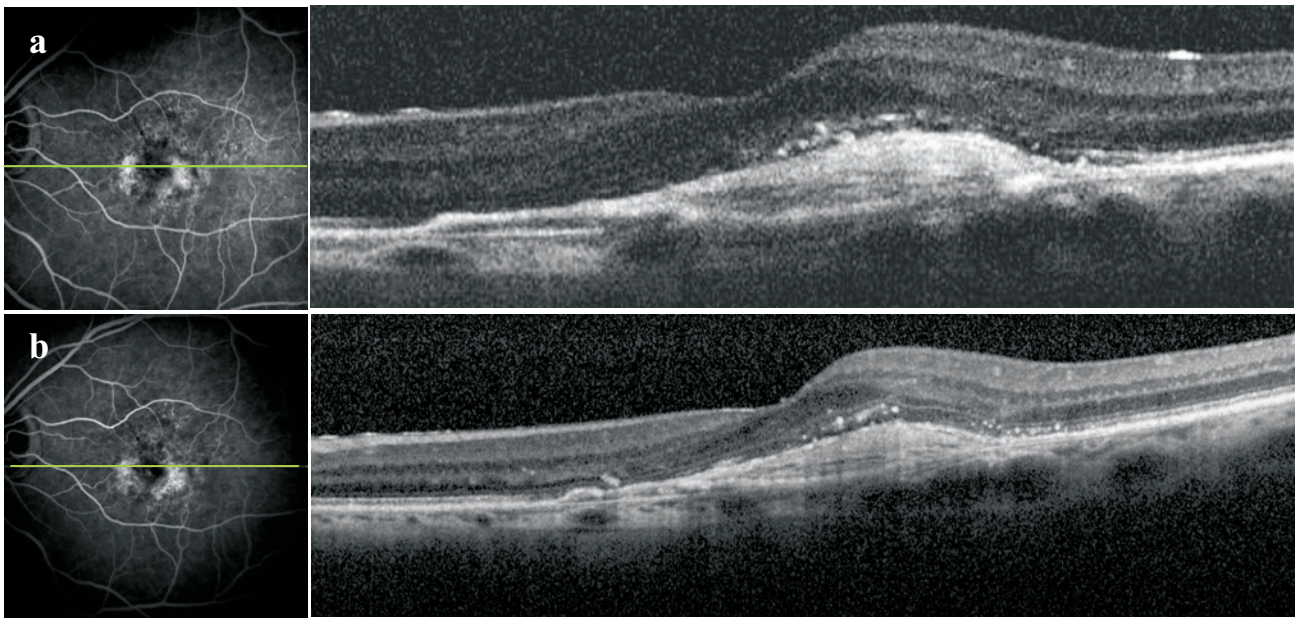


Figure 77: Bright hyper-reflective spots and dense zones.
***Spectralis** horizontal sections correlated with fluorescein angiography and ICG angiography** *(occult CNV during treatment)*.
SD-OCT: a): Before treatment, in the foveal zone, numerous bright hyper-reflective spots masking the IS/OS interface and external limiting membrane. These are located anterior to the vascularized PED, which is in the process of re-organizing. The outer nuclear layer is poorly visible. VA: 20/80.
b): After treatment, re-attachment and decreased thickness of the retina; reduction of bright hyper-reflective spots and restoration of the external limiting membrane and IS/OS interface. The outer nuclear layer is almost normal. VA: 20/40.

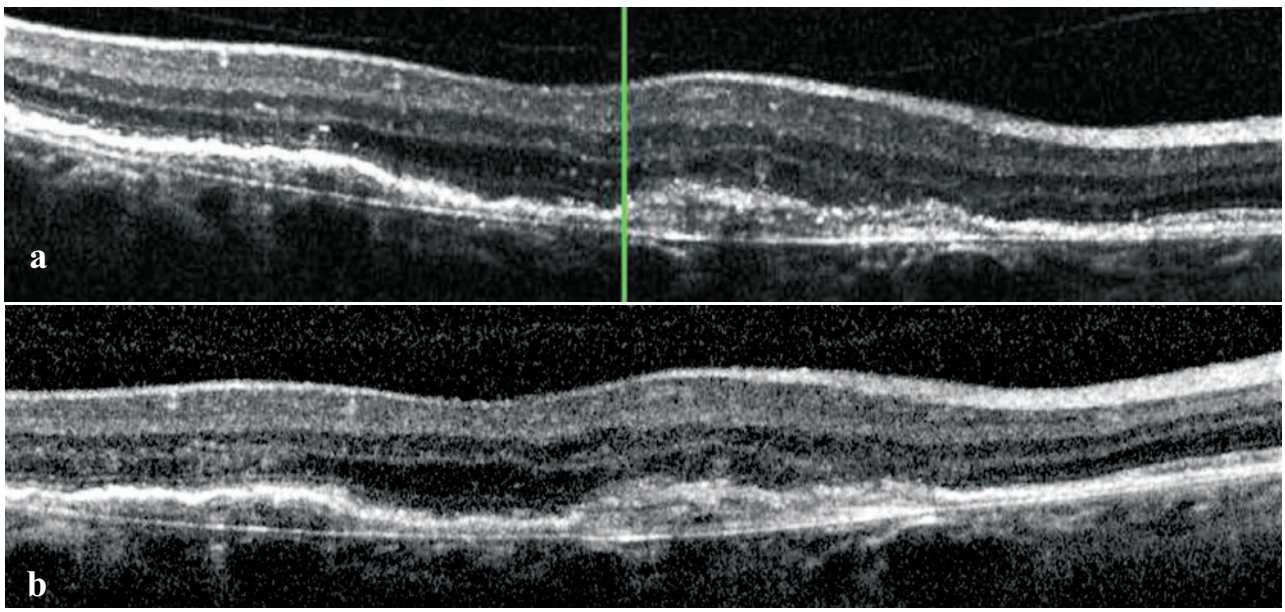
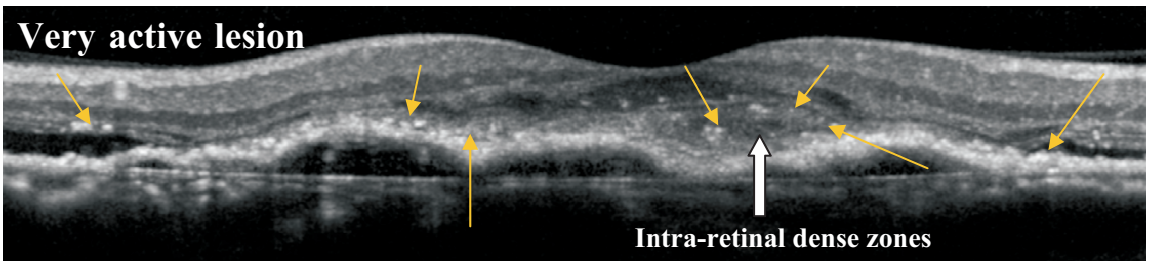


Figure 78: Bright hyper-reflective spots and dense zones.
***Spectralis** horizontal sections**: occult CNV with slightly raised but very extensive PED during anti-VEGF therapy.
SD-OCT: a): at the beginning of treatment, moderate diffuse intraretinal fluid with accumulation of bright hyper-reflective spots at the limits of this cystic space contiguous with the raised RPE. VA = 20/63.
b): After 3 IVT sessions, relative reduction of retinal thickness and the number of bright hyper-reflective spots. VA = 20/32.

BRIGHT HYPER-REFLECTIVE SPOTS AND DENSE ZONES



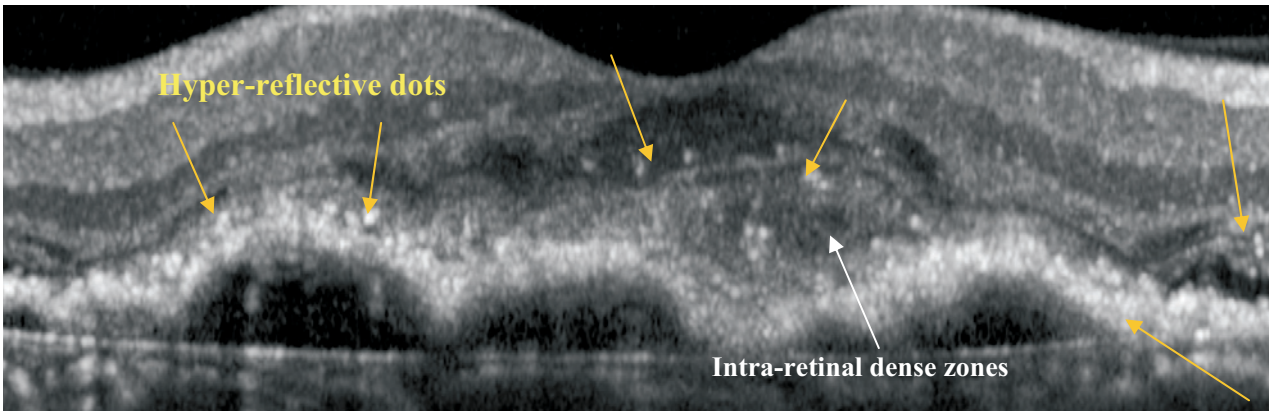


Figure 79: Bright hyper-reflective spots and dense zones.
***Spectralis** horizontal section**: advanced, extensive, irregular, wavy vascularized PED.
SD-OCT: thickened retina, raised by the vascularized PED. Numerous bright hyper-reflective spots, (yellow arrows), disseminated in the retinal tissue, predominantly in the outer layers, highlighting the limits of the IS/OS interface and external limiting membrane (which are poorly visualized).
Large zone of moderately reflective increased intraretinal density (white arrow) in the outer nuclear layer contiguous to the RPE. VA: 20/80.

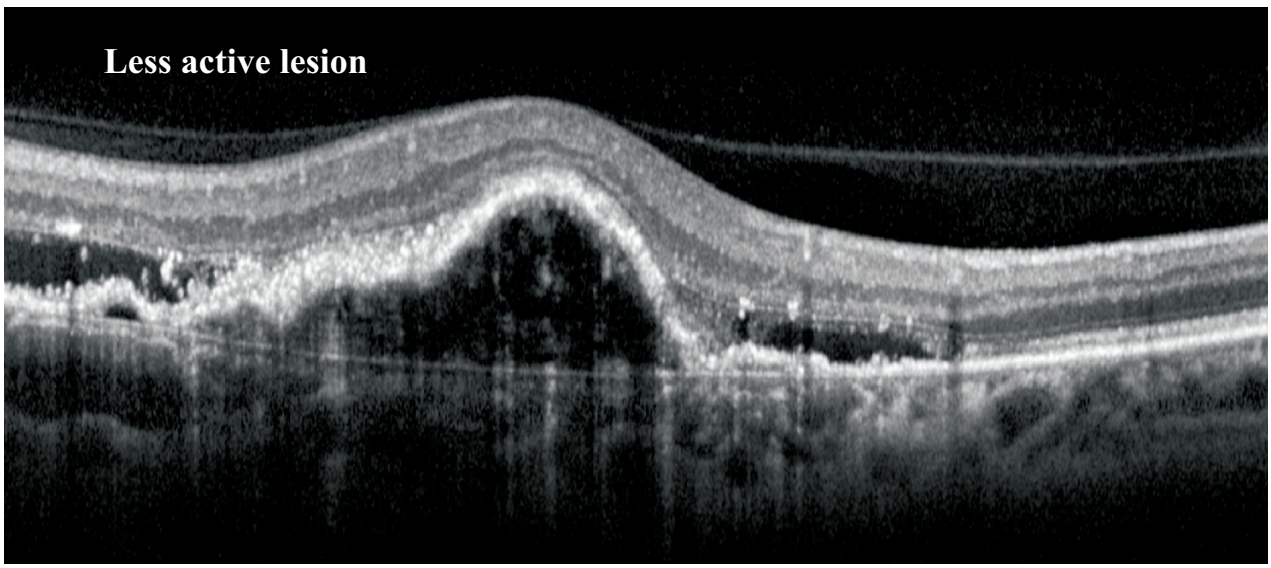


Figure 80: Bright hyper-reflective spots and dense zones.
***Spectralis** horizontal section**: advanced vascularized PED during anti-VEGF therapy.
SD-OCT: Progressive re-attachment of the retina which has resumed an almost normal configuration.
A large number of bright hyper-reflective spots persist, predominantly in the outer layers, highlighting the limits of the persistent SRD. The IS/OS interface and external limiting membrane are now visible and almost continuous. The outer nuclear layer remains poorly visible over the vascularized PED. VA: 20/40.

BRIGHT HYPER-REFLECTIVE SPOTS AND DENSE ZONES

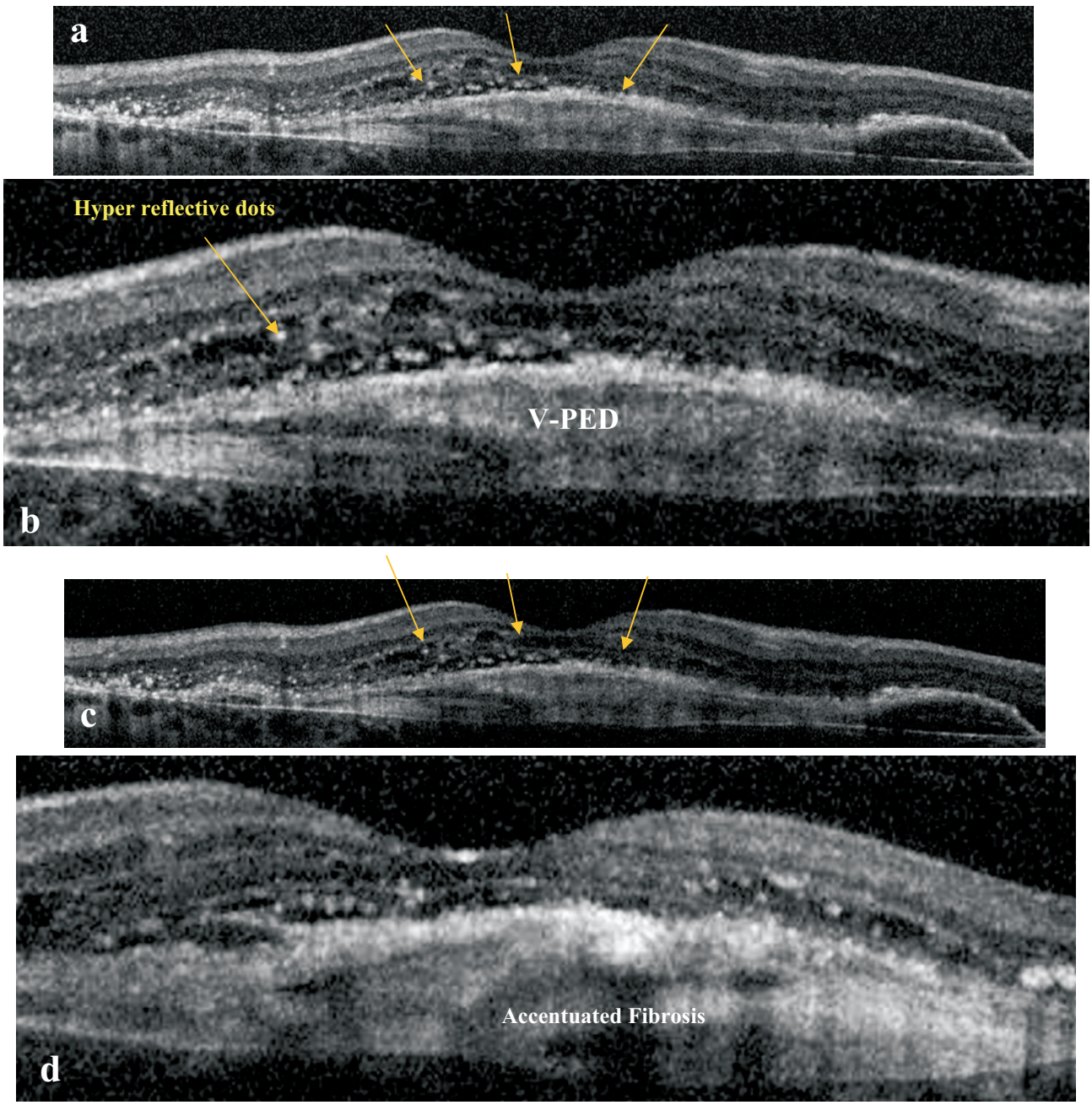


Figure 81: Bright hyper-reflective spots and dense zones: progression to fibrosis.

a and b): Before treatment: persistent vascularized PED progressing to fibrosis despite anti-VEGF therapy.

***Spectralis** SD-OCT horizontal sections**: advanced lesion with a very active appearance consisting of intraretinal fluid and numerous bright hyper-reflective spots. VA: 20/100.

c and d): After treatment: after 4 IVT sessions, persistence of the intraretinal fluid and bright hyper-reflective spots and accentuated hyper-reflectivity of the vascularized PED, suggesting progressive fibrosis and lack of response to treatment. VA: 20/200.

V. Anterior to the RPE: Retinal Hemorrhage

Choroidal neovascularization is frequently accompanied by retinal hemorrhage, responsible for characteristic signs and constituting one of the major elements of biomicroscopic examination. Retinal hemorrhages have a polymorphous appearance.

Large hemorrhages mask the neovascularization responsible for the bleeding and are difficult to interpret on angiography and sometimes even on indocyanine green angiography.

The exact site of the hemorrhage cannot always be easily determined, although some signs are very characteristic such as the hemorrhagic margin around classic CNV or the localized juxtafoveal retinal hemorrhage of chorioretinal anastomosis.

Spectral-Domain OCT is able to specify the site and extent of these hemorrhages and their relationship with CNV and can provide additional signs.

Four types of hemorrhages can be distinguished (**Figures 82-84**):

- **Group I**: hemorrhages accompanying occult choroidal neovascularization,
- **Group II:** hemorrhages accompanying chorioretinal anastomosis,
- **Group III:** hemorrhages associated with classic choroidal neovascularization,
- **Group IV:** hemorrhages complicating polypoidal choroidal vasculopathy.

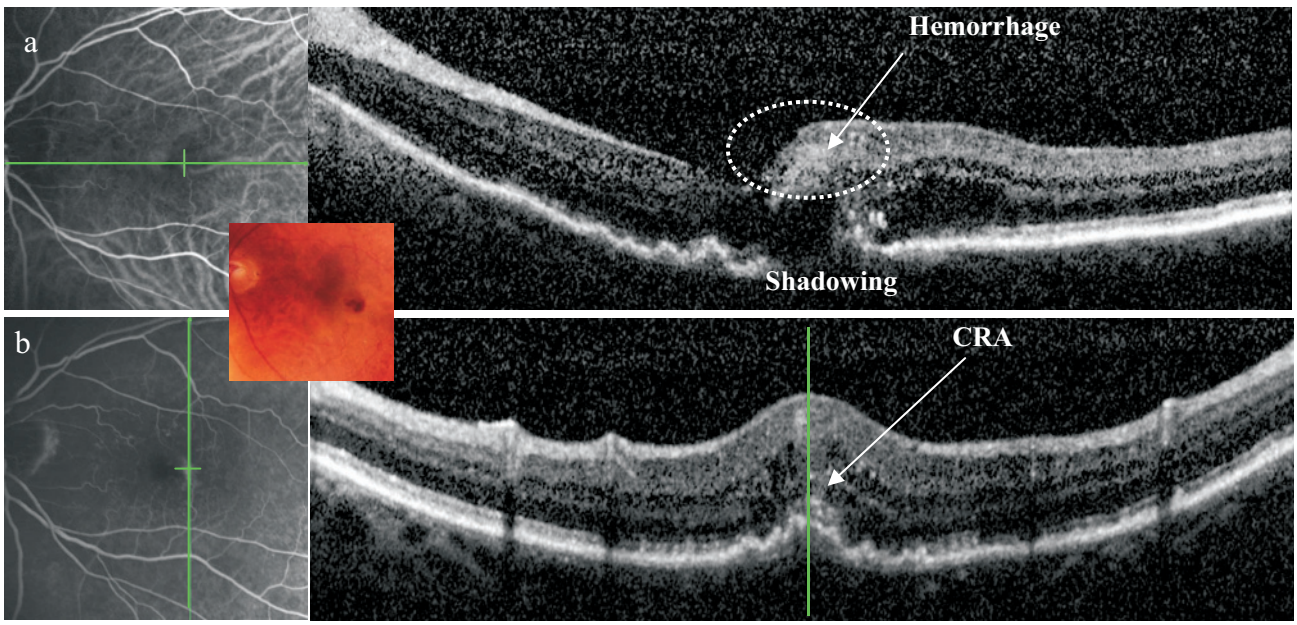


Figure 82: Retinal hemorrhage associated with chorioretinal anastomosis.

a): *Spectralis horizontal section correlated with ICG angiography**.
On SD-OCT, hemorrhage induces a denser and more hyper-reflective zone in the inner layers of the juxtafoveolar retina and is accompanied by back-shadowing with masking of all layers, including the RPE.

b): *Spectralis vertical section correlated with fluorescein angiography**: the green calliper is placed on fluorescein leakage partially masked by the hemorrhage.
The **SD-OCT** section passes adjacent to a hemorrhage and demonstrates a localized PED, the chorioretinal anastomosis, and intraretinal cysts.

RETINAL HEMORRHAGE

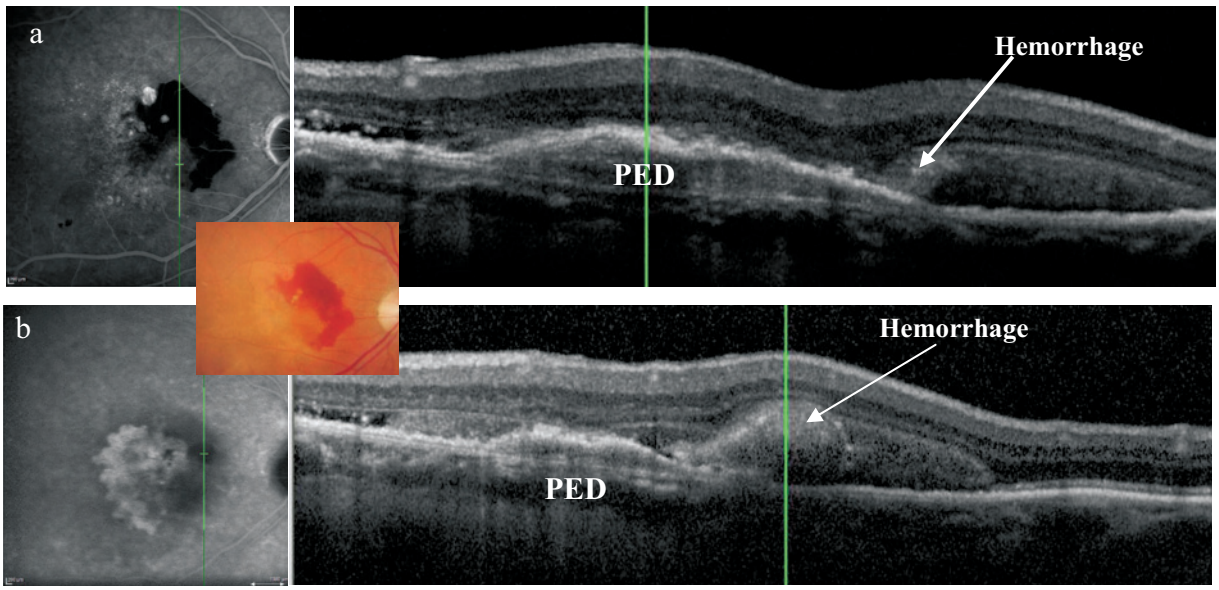


Figure 83: Retinal hemorrhage associated with an area of occult CNV.
a): *Spectralis vertical section correlated with fluorescein angiography**: nasal and superior arcuate hemorrhage partially masking the occult CNV.
On SD-OCT, clearly visible and well-delineated vascularized PED with fluid accumulation and bright hyper-reflective spots. In the superior half, the hemorrhage presents as a fairly dense, hyper-reflective zone between the outer layers of the retina and the RPE, causing partial back-shadowing.
b): *Spectralis vertical section correlated with ICG angiography revealing partially occult CNV.**
On SD-OCT, the section shows the inferior part of the PED, and a deep, fairly dense, hyper-reflective zone of hemorrhage between the outer layers and the RPE.
In the most dense zone, the light is blocked by the hemorrhage with a back-shadowing effect.

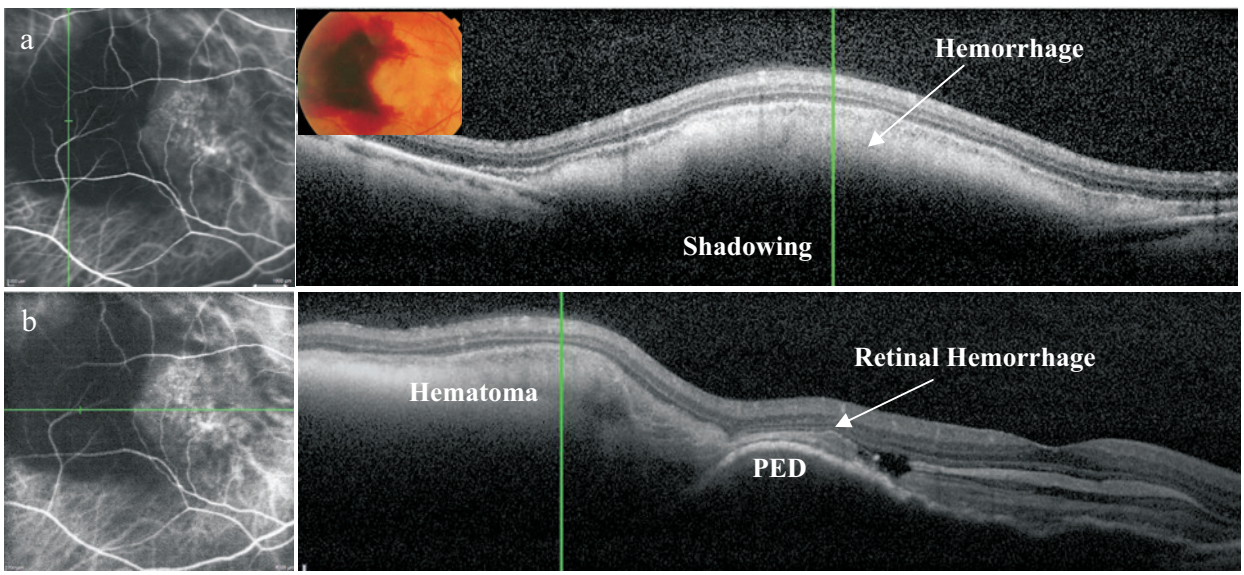


Figure 84: Macular hemorrhage associated with an area of occult CNV.
a): *Spectralis vertical section correlated with ICG angiography**: adjacent massive hemorrhage.
On SD-OCT, the hemorrhage infiltrates the outer retinal layers and completely masks the RPE and choroid.
b): *Spectralis horizontal section correlated with ICG angiography.**
On SD-OCT, the hemorrhage completely blocks the light causing back-shadowing. Note the changes in the outer retina layers anterior to the vascularized PED.

RETINAL HEMORRHAGE

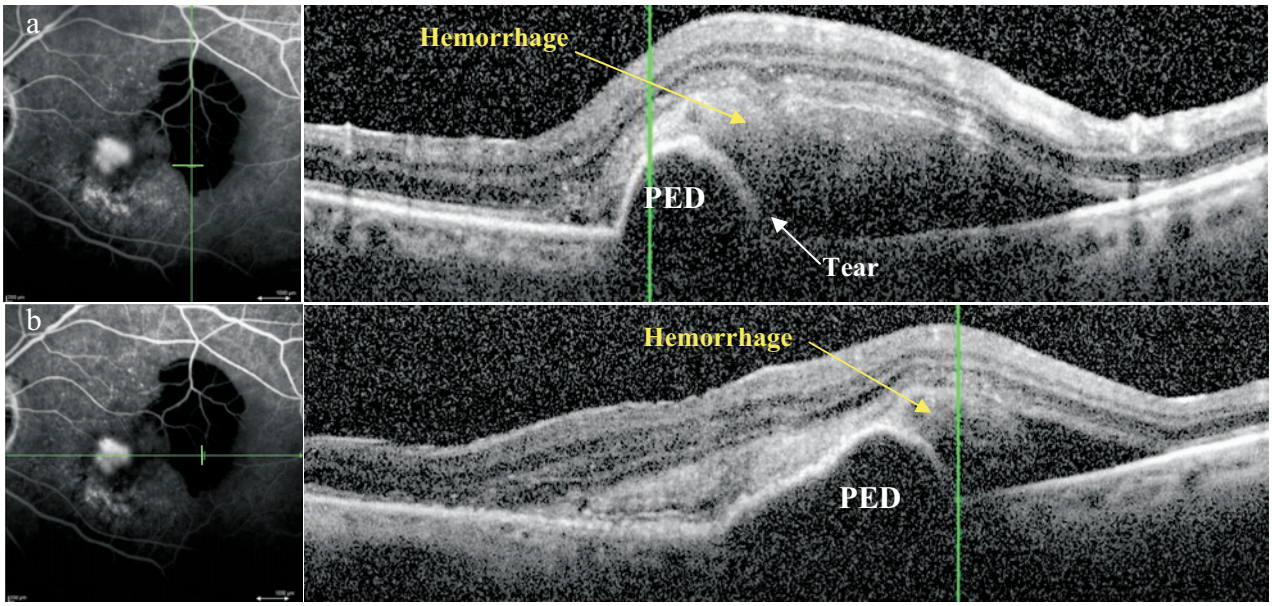


Figure 85: Arcuate hemorrhage associated with an RPE tear.

a): *Spectralis vertical section correlated with fluorescein angiography**: hemorrhage masking the tear.
SD-OCT: extensive hemorrhage anterior to the PED and anterior to the choroidal zone exposed by the tear.
b): *Spectralis horizontal section correlated with fluorescein angiography.**
On SD-OCT, the hemorrhage is visible as a white, hyper-reflective zone, partially blocking the light and causing back-shadowing.

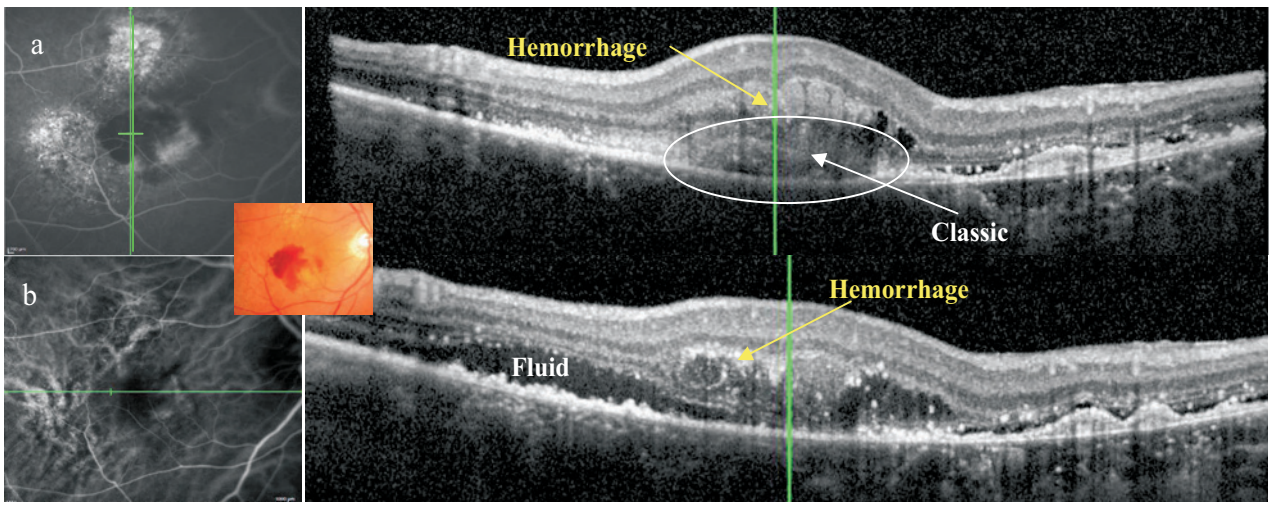


Figure 86: Retinal hemorrhage associated with classic CNV.

a): *Spectralis vertical section correlated with fluorescein angiography**: hemorrhage partially masking classic CNV.
SD-OCT: the hemorrhage is visualized as a dense, homogeneous, spindle-shaped zone in the outer retinal layers that lifts the retina. The hemorrhage is just anterior to and in contact with a classic CNV membrane proliferating anterior to the RPE. It induces changes of the IS/OS interface and outer nuclear layer with bright hyper-reflective spots and cysts.
b): *Spectralis horizontal section correlated with fluorescein angiography**. Same hyper-reflective appearance between the outer retinal layers and the altered IS/OS interface.