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Topographic angiography and optical coherence tomography: A correlation of imaging characteristics

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PURPOSE. *Topographic angiography (TAG) using confocal scanning laser angiography and optical coherence tomography (OCT) are new imaging modalities that have been introduced during recent years. OCT and TAG imaging were compared to specify the characteristics of each imaging modality.*
METHODS. *TAG using fluorescein angiography (FA) provides a three-dimensional profile of the vascular structures based on the analysis of a set of 32 confocal images over a depth of 4 mm. OCT provides cross-sectional images of the neurosensory retina and the retinal pigment epithelium-choriocapillary complex (RPE-CC). The authors compared and evaluated both modalities in 10 patients with predominantly classic choroidal neovascularization (CNV), 10 patients with serous pigment epithelial detachment (PED), and 10 patients with geographic RPE atrophy, all secondary to age-related macular degeneration (ARMD).*
RESULTS. *In patients with classic CNV, TAG detected neovascular structures and delineated their configuration. In PEDs pooling of extravascular fluid is demonstrated, and in geographic RPE atrophy TAG showed reduced choroidal perfusion. Classic CNV was demonstrated by OCT as a hyperreflective band at the level of the RPE-CC, and PED showed a dome-shaped RPE detachment. In geographic RPE atrophy, OCT imaged loss of the RPE band and had an increased depth resolution.*
CONCLUSIONS. *TAG and OCT are useful imaging modalities in the evaluation of ARMD cases. TAG visualizes the vascular configuration and dynamic perfusion and leakage changes. OCT is able to document intra-, subretinal, and sub-RPE fluid accumulation secondary to CNV. Both modalities may provide further valuable insight into ARMD pathogenesis, enhance diagnostic quality, and improve the assessment of therapeutic effects. (Eur J Ophthalmol 2005; 15:774-81)*

KEY WORDS. *Age-related macular degeneration, Choroidal neovascularization, Geographic atrophy, Imaging, Optical coherence tomography, Pigment epithelial detachment, Topographic angiography*

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INTRODUCTION

The current standard of vascular imaging in age-related macular degeneration (ARMD) is fluorescein angiography (FA) either using a standard fundus camera or a confocal scanning laser system for digital imaging.

However, standard angiography results in a two-dimensional image. Fluorescence phenomena are overlying each other and it is very challenging to detect precisely at which anatomic level pathologic changes are located and where leakage is originating from. Nevertheless, FA shows important details regarding the vascularization,

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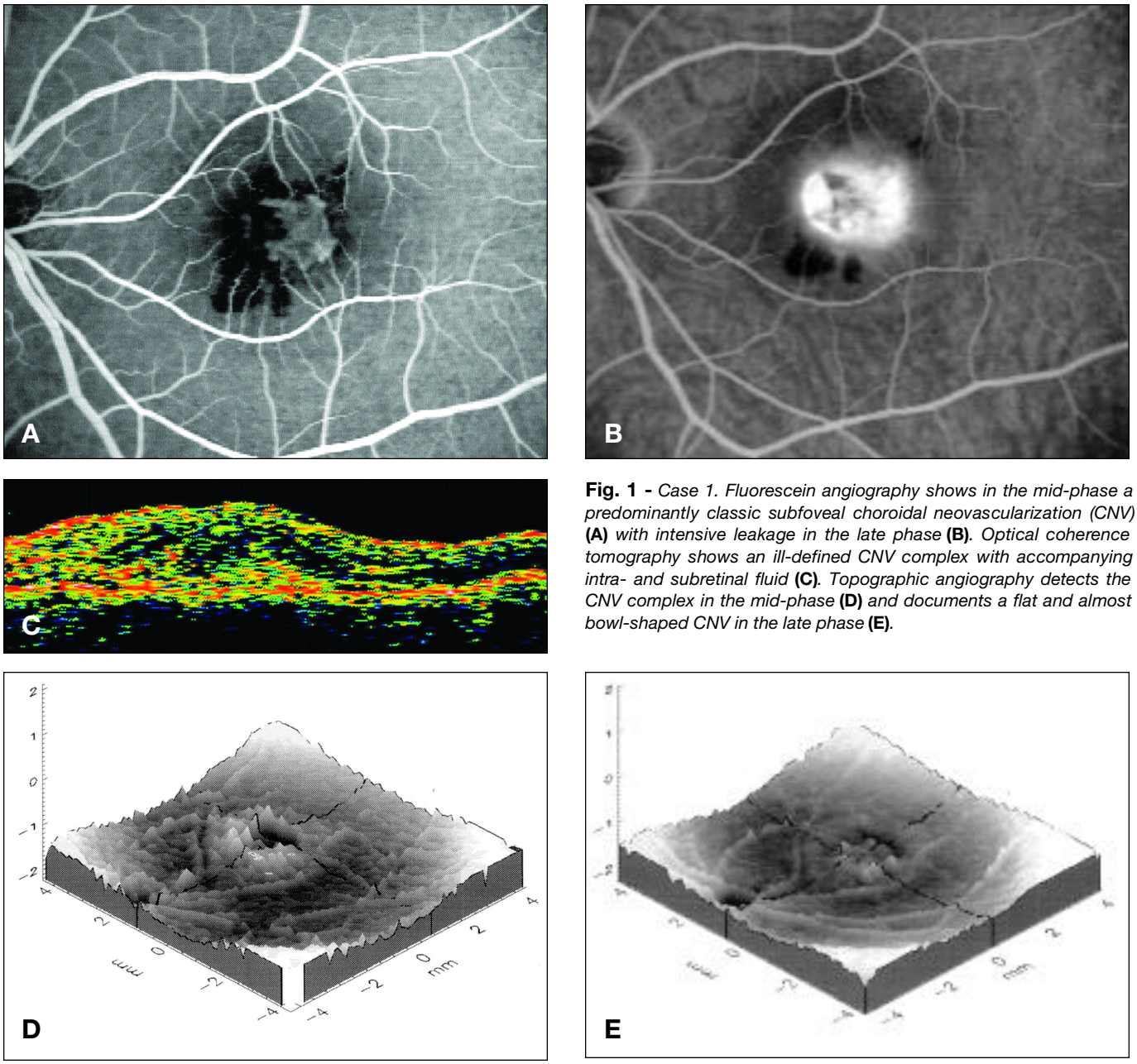

Fig. 1 - *Case 1. Fluorescein angiography shows in the mid-phase a predominantly classic subfoveal choroidal neovascularization (CNV)* **(A)** *with intensive leakage in the late phase* **(B)**. *Optical coherence tomography shows an ill-defined CNV complex with accompanying intra- and subretinal fluid* **(C)**. *Topographic angiography detects the CNV complex in the mid-phase* **(D)** *and documents a flat and almost bowl-shaped CNV in the late phase* **(E)**.

morphology, and leakage phenomena in ARMD. The introduction of topographic angiography (TAG) offers the three-dimensional profile of the fluorescent surface based on the analysis of a set of confocal images at different depth locations (1-4). In addition, the dynamic nature of perfusion in cases with choroidal pathologies like neovascular ARMD can be studied by comparing the fluorescence topography at different time points from dye injection (1-4).

Optical coherence tomography (OCT) is a well-established diagnostic tool that produces cross-sections of retina, RPE, and anterior choroid. It is used to analyze ARMD and its characteristic appearance (5, 6). In OCT, reflections from anatomic structures at different depths are displayed, creating a cross-sectional image. Major additional advantages of OCT are its noninvasiveness and the fast acquisition time. But OCT can be correlated to the depth-related topographic angiography. However, dynamic changes indicating lesion activity as in conventional FA or TAG cannot be displayed.

The goal of this study is to use topographic angiogra-

phy and OCT in cases with ARMD and compare the structural findings in OCT with perfusion-related details seen in TAG.

METHODS

Patients

All patients in this study presented with ARMD. Informed consent was obtained from all patients before any angiographic procedure was performed. The diagnosis of neovascular ARMD was based on standard fluorescein angiography using the Heidelberg Retina Angiograph (HRA, Heidelberg Engineering, Heidelberg, Germany). MPS criteria were used for FA evaluation in order to interpret FA (7). We analyzed 10 cases with predominantly classic CNV, 10 cases with serous pigment epithelial detachment (PED), and 10 patients with geographic atrophy secondary to ARMD.

No patient underwent prior laser treatment or showed substantial subretinal fibrosis.

Every patient was examined clinically by dilated indirect ophthalmoscopy using a 78-diopter Volk lens. Important clinical parameters like retinal thickening/edema; intraretinal-, subretinal-, and sub-RPE hemorrhage; subretinal fluid; subretinal fibrosis; or RPE changes were documented.

Topographic angiography and OCT were performed as described below.

Topographic angiography (TAG)

For TAG, FA using a confocal scanning laser angiograph (HRA, Heidelberg Engineering) was performed. Fluorescein (Alcon Pharma GmbH, Freiburg, Germany) was given as a bolus injection.

Data acquisition

A series of 32 confocal fluorescence images with a depth separation of 125 mm were taken, comprising a total depth of 4 mm. The first series was taken at 60 to 80 seconds and the second 15 minutes after bolus fluorescein injection. The images had a field of view of 30 degrees and a resolution of 256*256 pixels. Acquisition of each series took 1.5 s, or 32 ms per image. The diameter of the scanning excitation beam at a wavelength of 790 nm was specified to be 15 µm at the retina. The nominal diffraction-limited Rayleigh range of the focal beam waist, defined by the axial depth resolution, was 400 µm.

Data processing

For data processing proprietary software was used. The 32 images of a complete series were aligned with respect to the middle image using a standard cross-correlation technique in the Fourier domain; translatory and rotational eye movements and other misalignments were corrected.

The aligned 32 images are then projected on top of each other and displayed as a fluorescence intensity image corresponding to a standard FA image: areas with intense fluorescence appear bright, areas with low levels of fluorescence are shown dark.

In order to obtain the topographic profile of the fluorescent structure, the proprietary software analyzed the axial course of the fluorescence intensity at each lateral location (pixel). The depth of the topographically relevant surface structure at each pixel was defined as being the location where the fluorescence intensity reaches 75% of the maximum within the axial scan.

Finally, this two-dimensional grayscale-coded height profile of the fluorescence surface is displayed as a three-dimensional topographic image. For further detail of the TAG technique, see references 1 to 3.

Optical coherence tomography

The basic principle behind OCT is interferometrically measuring the reflected light from different depths of the tissue separately. A sequence of those optical A-scans is then combined by lateral scanning into a cross-sectional B-scan image of the retina and the RPE-choriocapillary complex. For our study we used the Zeiss-Humphrey OCT model 2010 with an axial resolution of 10 to 20 µm as well as an 840 nm slit-lamp adapted OCT with an axial resolution of 14 µm (8).

The documented OCT scans were taken FA-guided. Vertical scans right through the center of the ARMD lesion shown by late phase FA were performed.

RESULTS

Topographic angiography and OCT were used to examine 30 eyes divided in patients with classic CNV (n=10), 10 eyes with a serous PED, and 10 patients with geographic RPE atrophy all secondary to ARMD. The average age of the patients was 71 years; 21 patients were female and 9 male.

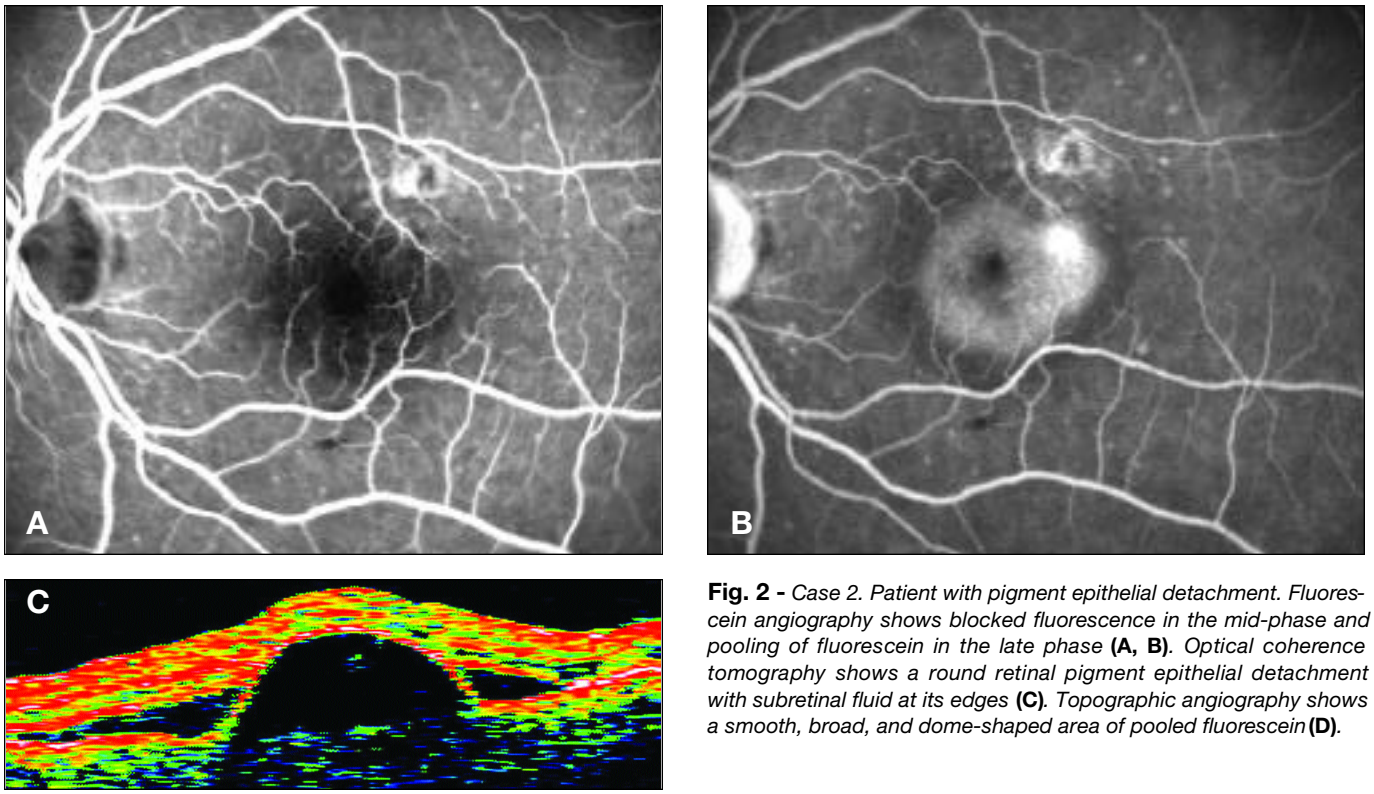

Fig. 2 - *Case 2. Patient with pigment epithelial detachment. Fluorescein angiography shows blocked fluorescence in the mid-phase and pooling of fluorescein in the late phase* **(A, B)**. *Optical coherence tomography shows a round retinal pigment epithelial detachment with subretinal fluid at its edges* **(C)**. *Topographic angiography shows a smooth, broad, and dome-shaped area of pooled fluorescein* **(D)**.

Correlation of topographic angiography and OCT

In terms of detection of a neovascular complex both modalities have complementary capabilities. OCT detects the site of the neovascular complex, and associated accumulation of fluid with subretinal, intraretinal, or sub-RPE location.

Topographic angiography detects neovascular structures. Moreover, topographic angiography displays the height of perfused structures in respect to the choriocapillary environment. In normal retina the maximum of fluorescence is found at the choriocapillary level. A characteristic finding is that predominantly classic CNV have a rather flat and bowl-shaped appearance with a prominent rim.

The configuration of the neovascular complex differs from the appearance on OCT. In cases of classic membranes no well-defined structure was seen by OCT compared to TAG. By OCT the complex is rather diffuse or fusiform.

Another correlation category is visualization of phenomena that occur secondary to CNV such as intra-, subretinal, and sub-RPE fluid extravasation.

By OCT intra-, subretinal, and sub-RPE fluid is identified and can be quantified. However, OCT cannot differentiate between an inactive lesion with chronic fluid and an active lesion with new onset fluid accumulations. Apart from PEDs, leakage of fluorescein is not detected well by TAG. A typical finding in TAG is that in late phase images neovascular lesions usually appear smaller and much more delineated than lesions imaged 60 to 80 seconds after injection of fluorescein. This is also a key difference to standard FA where CNV borders usually fade during the late phase due to leakage of fluorescein.

In cases with geographic RPE atrophy, OCT images might produce misleading information. The hyperreflective band represents the anterior choroid in this pathology. This should not be mistaken as fibrotic tissue due to an inactive CNV complex. Furthermore OCT is not able to document RPE atrophy associated changes in the choriocapillaris. In contrast, topographic angiography clearly shows a profoundly reduced choroidal perfusion in the area of RPE atrophy, indicated by a shift of max fluorescence to the deep choroid.

TAG is therefore able to give useful information about the choriocapillary perfusion without the need for an additional invasive and expensive ICG angiography.

Case reports

Case 1. A patient presented with classic CNV secondary to ARMD on standard FA. The lesion is well demarcated in the early phase with some subretinal blood and shows significant leakage in late phase of FA (Fig. 1, A and B).

TABLE I - TYPICAL FINDINGS ON OPTICAL COHERENCE TOMOGRAPHY (OCT) AND TOPOGRAPHIC ANGIOGRAPHY (TAG) WITHIN EACH GROUP

		OCT		TAG
Classic CNV (n=10)	Retina	Retinal thickening, often associated with intraretinal cysts and subretinal fluid	Retina	Only vascular structures or fluorescein filled spaces can be outlined
	RPE	Focal thickening and irregularities in RPE continuity	RPE	Cannot be evaluated
	Choroid	The choroidal neovascularization itself cannot be differentiated from surrounding tissues	Choroid	Well-defined neovascular complex with characteristic changes over time
Serous PED (n=10)	Retina	No retinal thickening; centrally attached to RPE	Retina	Only vascular structures or fluorescein filled spaces can be outlined
	RPE	Regular shaped detachment	RPE	Cannot be evaluated
	Choroid	Masked by the hyperreflective RPE band and the overlying serous fluid	Choroid	Dome-shaped and regular pattern of the posterior pole, sharp margins, often central plateau in late phase TAG
Geographic RPE atrophy (n=10)	Retina	Atrophy and thinning	Retina	Only vascular structures or fluorescein filled spaces can be outlined
	RPE	Atrophy and thinning	RPE	Cannot be evaluated from deeper choroids, no information on vascular structures
	Choroid	Increased signals from deeper choroids, no information on vascular structures	Choroid	Well-defined perfusion defect; maximum of fluorescence in deep choroid indicating loss of choriocapillary

CNV = Choroidal neovascularization; RPE =Retinal pigment epithelium

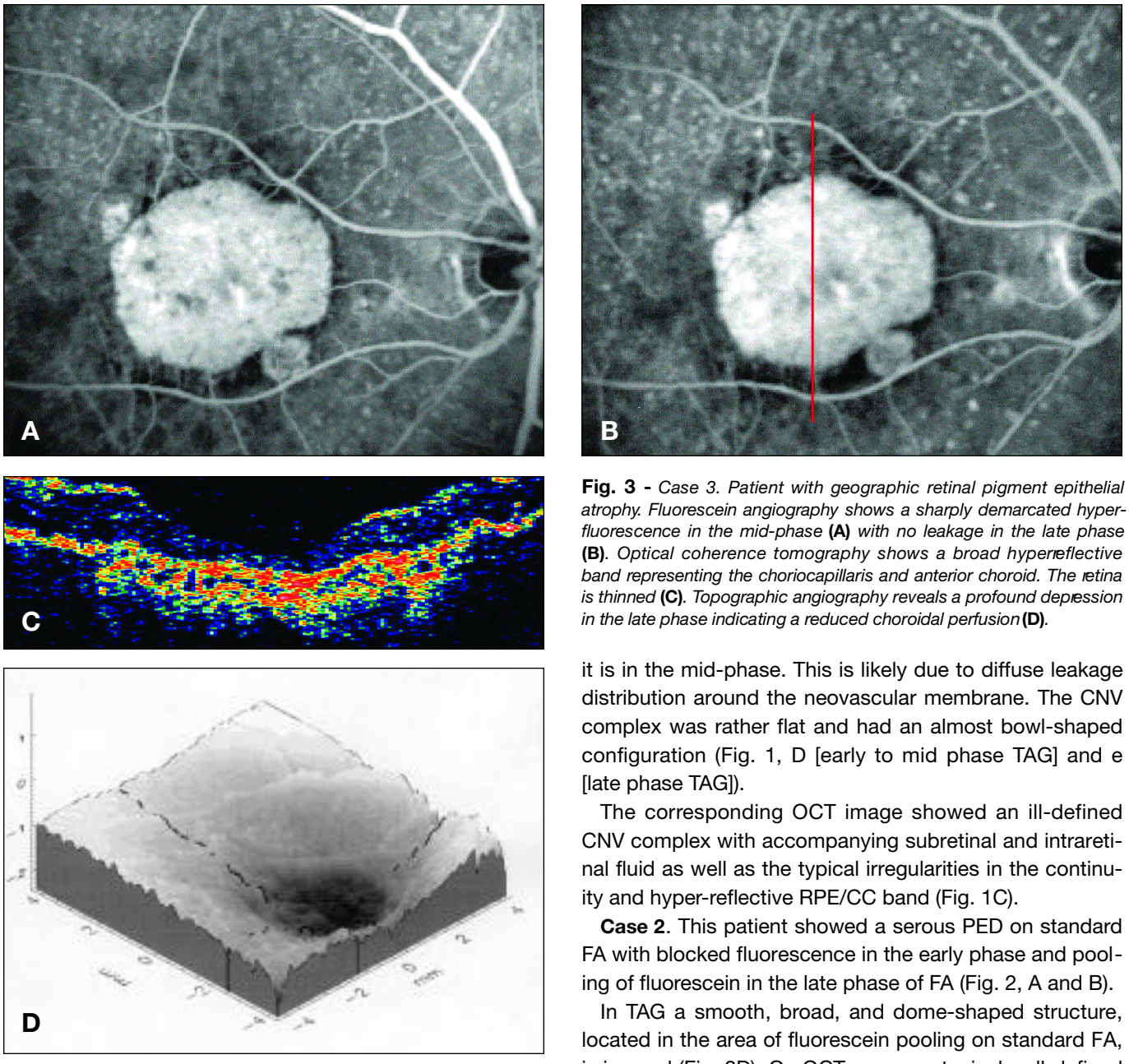

Fig. 3 - *Case 3. Patient with geographic retinal pigment epithelial atrophy. Fluorescein angiography shows a sharply demarcated hyperfluorescence in the mid-phase* **(A)** *with no leakage in the late phase* **(B)**. *Optical coherence tomography shows a broad hyperreflective band representing the choriocapillaris and anterior choroid. The retina is thinned* **(C)**. *Topographic angiography reveals a profound depression in the late phase indicating a reduced choroidal perfusion* **(D)**.

By TAG, three important structures are detected: the optic disc, the temporal vascular arcades, and the subfoveal neovascular complex. The irregular shaped surface and the subfoveal neovascular complex was imaged during the series performed 60 to 80 seconds after injection of the dye. The elevated margins showed an increased level of fluorescein appearance while a central perfusion defect could be seen. In the late phase the surface configuration appeared more regular but a central perfusion defect could still be observed but is not as impressive as it is in the mid-phase. This is likely due to diffuse leakage distribution around the neovascular membrane. The CNV complex was rather flat and had an almost bowl-shaped configuration (Fig. 1, D [early to mid phase TAG] and e [late phase TAG]).

The corresponding OCT image showed an ill-defined CNV complex with accompanying subretinal and intraretinal fluid as well as the typical irregularities in the continuity and hyper-reflective RPE/CC band (Fig. 1C).

Case 2. This patient showed a serous PED on standard FA with blocked fluorescence in the early phase and pooling of fluorescein in the late phase of FA (Fig. 2, A and B).

In TAG a smooth, broad, and dome-shaped structure, located in the area of fluorescein pooling on standard FA, is imaged (Fig. 2D). On OCT we see a typical well-defined RPE detachment, a hyporeflective area suggesting sub-RPE serous fluid in the sub-RPE space, and some subretinal fluid at the margins of the RPE detachment. On top of the RPE detachment the retina is flat and attached to the RPE (Fig. 2C).

Case 3. FA of this patient documented RPE atrophy. A bright and well-demarcated hyperfluorescence in the early phase is noted, which is due to a window defect caused by RPE atrophy. During late phase FA no leakage occurred (Fig. 3, A and B).

In TAG a profound central depression is documented in the area of geographic atrophy of the RPE indicating a maximal fluorescence at the deep choroidal level and a substantial reduction of choriocapillary perfusion (Fig. 3D).

OCT reveals a broad hyperreflective band representing the choriocapillaris and the anterior choroid. These structures are enhanced because RPE atrophy leads to an optical window phenomenon. However, no information is provided on the choroidal vascular structure (Fig. 3C). Reduced retinal thickness, secondary to RPE atrophy, is detected by OCT.

DISCUSSION

TAG using confocal scanning laser angiography and OCT are new imaging modalities that have been introduced during recent years (1-4, 8). In this study we concentrated on cases with ARMD and correlated TAG findings to OCT images.

TAG deducts its image information from perfused vascular structures. The system analyses the depth profile of fluorescence intensity for each image pixel, where the topographically relevant fluorescence intensity in the currently used software is defined as being 75% of the fluorescence intensity maximum for each axial scan. In detail, the software creates a topography of the 75% values of maximum fluorescence intensity for each pixel. The resulting fluorescence topography does not display pure anatomy. It rather is an image on the basis of a fluorescence pattern which has its origin in perfused chorioretinal vasculature.

In OCT, however, morphologic structures with their modified light scattering properties independent of their perfusion status play the leading role.

From a practical point of view, the characteristics of TAG have advantages and disadvantages. The advantage in active, predominantly classic CNV is that the diffuse leakage occurring in the late phase of FA does not obscure CNV structures and borders due to the 75% algorithm included in the TAG software. Fluorescence intensity in these areas of diffuse leakage is not detected, because the intensity at a distinct point is too low to fulfill the 75% criterion. This is a unique difference compared to standard FA and provides valuable information especially during follow-up controls regarding the perfusion pattern of predominantly classic lesions. This phenomenon also explains why CNV structures seem to be less extensive in the late phase TAG, when compared to the TAG pictures 60 to 80 seconds after injection of the dye. In these early to mid-phase images fluorescein leakage from the neovascular membrane is still concentrated in the tissue surrounding the membrane. Here, the intensity of fluorescein activity is much higher than it is in the late phase TAG. Due to this TAG characteristic, the CNV lesions seem to be more extensive in the early to mid-phase TAG than they appear in the later phases. In conclusion, TAG gives valuable information about the neovascular perfusion pattern, size, and configuration in predominantly classic CNV. However, changes of the retinal structure or the exact anatomic level a detected defect belongs to cannot be given by TAG examination. This missing information is added by OCT in a complementary way. With OCT intra-, subretinal, or sub-RPE changes like cysts or free fluid can be outlined clearly with a high reproducibility. OCT adds information about changes down to the level of the RPE. A fusiform thickened, irregular structure in the RPE band that appears on OCT images can often be seen in eyes with predominantly classic CNV. On the other hand, OCT provides no information on the vascular barrier function or the question whether intra-, subretinal, or sub-RPE fluid comes from an acute or chronic process. The neovascular membrane itself also cannot be outlined reliably due to the constantly improving but still not sufficient resolution of OCT systems and the fact that the neovascular membrane is often masked by the hyperreflective fibrotic retinal tissue overlying the neovascular complex. Further improvement of OCT technology is necessary to obtain more information on neovascular structures.

In PED TAG outlines a dome-shaped change in the perfusion pattern of the posterior pole. This pattern shows the fluorescein molecules pooling underneath the level of RPE. The fluorescence intensity reaches the 75% intensity cut off directly underneath the level of RPE in late phase TAG. However, like in predominantly classic CNV, the anatomic level of the defect is better identified by OCT. OCT shows the retina attached to the RPE with subretinal fluid only at the margins of the lesion. With this information obtained by OCT, the fluid pooling seen in TAG has to be underneath the level of RPE, which matches with the known pathophysiology.

In geographic atrophy TAG outlines a perfusion defect in the fluorescence pattern of the posterior pole. These images explain the window in conventional FA three dimensionally. Maximum fluorescence in geographic atrophy has shifted from the choriocapillary to the deeper

choroid, indicating a loss of perfusion in the choriocapillary. TAG outlines this phenomenon in contrast to the "unaffected" surrounding choriocapillary. OCT examination lacks information about the choroidal perfusion despite an increased signal from the choroidal level due to RPE loss in the affected area. However, OCT frequently shows a thinning of the retina overlying the defect.

In conclusion, TAG has been shown to be a very promising tool in imaging ARMD pathology. In contrast to standard FA, the activity of the neovascular lesions can be assessed by the analysis of the configuration of the neovascular complex. TAG allows interpreting leakage pattern differently from standard FA. Diffuse late leakage, due to its low intensity profile, is not obscuring the CNV outlined in late phase. High intensity profile leakage just around the CNV, however, plays an essential role and explains why the lesion complex in early-mid phase TAG is larger than in late phase TAG. Further investigation is necessary to compare early (20 to 30 sec) to early-mid phase (60 to 80 sec) and late phase TAG (15 min).

Moreover, TAG allows an evaluation of choroidal perfusion in cases with dry ARMD. This is particularly interesting in terms of pathophysiologic considerations. Certain aspects of TAG using fluorescein could to some extent be shown by indocyanine green angiography (ICGA) using a scanning laser ophthalmoscope (SLO), however, three-dimensional information is missing and an additional angiography is necessary.

OCT as an established diagnostic tool in macular pathology has demonstrated its ability to image morphologic changes due to CNV, such as intra-, subretinal, and sub-RPE fluid accumulation. TAG and OCT do not replace biomicroscopy and standard FA. However, a combination of different imaging modalities will provide further valuable insight into ARMD pathogenesis, enhance diagnostic quality, and improve the assessment of therapeutic effects.

None of the authors has any financial interest in the subject matter.

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