Optical Coherence Tomography Angiography versus Fundus Fluorescein Angiography in Assessing Age-Related Macular Degeneration: A Retrospective Study

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Original Research Article

ABSTRACT

Optical coherence tomography angiography (OCTA) could be a valid tool to detect choroidal neovascularization (CNV) in neovascular age-related macular degeneration (nAMD), allowing the analysis of the type, the morphology, and the extension of CNV in most of the cases. This retrospective cross-sectional study, aimed to highlight the role of optical coherence tomography angiography (OCTA) as compared to fluorescein angiography (FA) in the evaluation of age related macular degeneration (AMD).was conducted at tertiary eye care centre. This study enrolled 24 patients (48 eyes). All patients underwent swept-source optical coherence tomography (SS-OCT), swept-source OCTA, and fundus fluorescein angiography (FFA). OCTA was used to evaluate neovascular networks in terms of their type, location and extent of visualization. Sensitivity and specificity of the method were assessed based on FFA diagnosis as the gold standard. In our study, the sensitivity and specificity of OCTA in detecting CNV secondary to wet AMD seem to be high which were 85.1% and 80% respectively. OCT angiography is a clinically useful tool to evaluate the CNV activity and response to treatment as well as to differentiate the various types of CNV in wet AMD.

KEY WORDS: age-related macular degeneration (AMD), choroidal neovascularisation (CNV), flourescein angiography (FA), optical coherence tomography angiography (OCTA)

INTRODUCTION:

Age-related macular degeneration (AMD) is the term applied to ageing changes in macula without any other obvious precipitating cause in people aged 50 years and above[1]. Aging is the strongest risk factor for AMD. Age-related changes in Bruch's membrane and age-related formation of the components of drusen play the strongest role in AMD[2]. AMD has been classified depending on whether there is a presence of abnormal neovascularization into wet (exudative or neovascular) and dry AMD[3].

Neovascular age-related macular degeneration (nAMD), also known as wet age-related macular degeneration, an advanced form of macular degeneration, is the leading cause of visual impairment in older adults related to AMD[4]. The presence of abnormal blood vessels, known as choroidal neovascularization (CNV), can penetrate Bruch's membrane (BM) and extend into the subretinal pigment epithelial (RPE) or subretinal space. CNV can induce haemorrhage, fluid exudation, and fibrosis, resulting in photoreceptor damage and vision loss[5]. Aging is the strongest risk factor for AMD, but is not modifiable. Early visualization and diagnosis of the CNV lesion are essential to prevent progressive, irreversible vision loss.

As the current gold standard of determining the presence of leakage on fluorescein angiography (FA) can provide dynamic information[6]. In the late phase of the angiogram leakage of dye is used to diagnose and classify CNV as classic, occult, or combination subtype. However, it is an invasive procedure, requiring intravenous dye injection, which can induce nausea, discomfort, and occasionally anaphylaxis[7,8]. In addition, this technique is time consuming, taking about 15–20min to complete, which can limit its routine use in a busy clinical setting.

For these reasons, optical coherence tomography (OCT) was introduced. OCT has become a widely used non-invasive imaging technique these days to detect the presence and activity of CNV without the use of intravenous dye. It enables

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visualization of the morphological features of the fibrovascular complex and the exudative consequences of fluid accumulation, which is accompanied by retinal thickening and edema[9]. However, sensitivity of OCT is only to the backscattering light intensity and can't distinguish vasculature from fibrous and other surrounding tissues. Because of this limitation, it is very difficult to recognize the the precise location and activity of the CNV. Thus, OCT imaging cannot replace but supplement FA in the diagnosis of nAMD[10].

Optical coherence tomography angiography (OCTA) is a novel imaging modality that allows direct visualization of the retinal and choroidal vasculature in vivo. In OCTA, high-frequency and dense volumetric scanning are applied to detect blood flow by analysing the signal decorrelation between scans. Compared with stationary areas of the retina, the movement of erythrocytes within a vessel generates a decorrelated signal[11]. Unlike traditional angiography, OCTA does not require the use of exogenous dyes, thus avoiding potential side effects, such as nausea or other more serious adverse events.

However, the role of OCTA in diagnosing neovascular age-related macular degeneration has not been widely investigated. Very few clinical studies [12] have evaluated the accuracy of OCTA imaging for the diagnosis of nAMD. Therefore, this study was conducted to evaluate the efficacy of OCTA in detecting nAMD.

MATERIAL AND METHODS:

A retrospective cross-sectional review based analysis of data was done at Retina Institute of Karnataka, Bangalore during usual clinical practice from consecutive patients diagnosed with nAMD. Clinical and instrumental assessments were performed in 24 patients (48 eyes). The subjects included in this study were patients over 50 years with clinical features of age-related maculopathy, such as soft or hard drusen, pigmentary alterations and macular exudative signs on FFA.

All the patients underwent a comprehensive eye examination, which included slit lamp biomicroscopy, colour fundus photography, swept source OCT (SS-OCT) and swept source OCTA (SS-OCTA) using Topcon OCT Triton. The angioretina of the Topcon OCT Triton utilizes OCTARA algorithm. OCTA acquisition protocol in the macular region consisted of a 6×6 mm area centred onto the fovea. En face OCTA images were segmented into four layers, namely the superficial vascular plexus, deep vascular plexus, outer retina, and choriocapillaries. Exclusion criteria were (a) patients without OCTA or FA results available for analysis or ,patients with CNV secondary to pathological myopia, angioid streaks, chorioretinitis, central serous chorioretinopathy, tumors, or trauma; (b) media opacities, such as cataracts, (c) preventing detailed imaging, history of posterior segment surgery within the last 6 months, history of laser photocoagulation and (d) any contraindication to intravenous fluorescein injection as renal impairment and hypersensitivity.

For FA, according to the criteria of the Macular Photocoagulation Study[13,14], the CNV lesions were graded as classic, occult, and combination. Classic CNV was defined as an area of uniform and early (<30 sec) hyperfluorescence leakage throughout the middle and late phases. Occult CNV was identified by fibrovascular pigment epithelial detachment (stippled hyperfluorescence) or latephase leakage of an undetermined source. The appearance of CNV on the OCTA images and coregistered corresponding OCT B-scans was assessed, in addition to the presence of subretinal fluid, intraretinal fluid, or sub-RPE fluid. CNV was defined as the presence of a decorrelation signal at the outer-retina level on OCTA consistent with the vascular component of the lesion. The appearance of CNV on an OCTA image was classified as either well circumscribed (lacy wheel or sea fan-shaped vessels) or poorly circumscribed (long filamentous vessels).

All statistical interpretation and analysis of results obtained were carried out using statistical software SPSS version 22 (Statistical Package for Social Sciences, version 22, SPSS Inc, Chicago, IL, USA) and Microsoft Excel.

RESULTS:

We reviewed 24 patients (48 eyes) with macular degeneration who visited the Institute. Eleven eyes were excluded because of poor quality images attributable to poor fixation, media opacity, absence of OCTA or FA results. 37 eyes of 24 patients were assessed. The patients consisted of 15 men and 9 women aged between 50 and 85 years with mean age, 67 years (Table 1). 27 eyes were diagnosed as having CNV with FA, with 3 patients diagnosed as having bilateral nAMD. According to FA, the CNV lesions were classified as classic in 14 eyes, occult in 11 eyes. And mixed in 2 eyes.

The qualitative tomographic OCTA review showed signs of CNV in 23 eyes. Occult CNV lesions (type I on OCT) were best visualized on the SS-OCTA

Table 1: Demographic and clinical data of the study patients.

Gender		
	Male	15
	Female	9
Age		
	Mean	67
	SD	10.3
	Min	50
	Maximum	85
AMD Classification		
	Classic	14
	Occult	11
	Mixed	2

Table 2: Detection of eyes with neovascular age-related macular degeneration using optical coherence tomography angiography compared to fluorescein angiography.

	Fluorescein Angiography		
OCTA	Positive	Negative	Total
Positive	23	2	25
Negative	4	8	12
Total	27	10	37

Table No.3 Sensitivity, specificity, and predictive value of SSOCTA in detecting neovascular age related macular degeneration.

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
OCTA	85.1	80	92	66.6

en face projection of the choriocapillaris, whereas classic CNV lesions (type II on OCT) were best visualized on the SS-OCTA en face projection of the outer retina. Mixed CNV lesions can be seenon the SS-OCTA en face projection of both the outer retinaand choriocapillaries layer (Figure 1). OCTA enabled accurate localization of neovascular networks with respect to the RPE layer. 2 false-positive cases were observed on OCTA (Figure 2), (Table 2). There were 4 false-negative cases (Figure 3). The specificity of OCTA for the detection of CNV was 80%, with a sensitivity of 85.1% and positive and negative predictive values of 92% and 66.6%, respectively (Table 3).

DISCUSSION:

FA can detect dynamic patterns of dye transit and leakage and keeps the current gold standard for diagnosing CNV[6]. However, traditional angiography is invasive and time consuming. Other major limitations are that it provides only a two-dimensional image and cannot directly visualize nascentvessels. SD-OCT is increasingly used in clinical practice to determine both the presence and activity of CNV. It can not replace FA as the gold standard in the diagnosis of nAMD, because the reflectivity of CNV tissue and drusenoid material, hemorrhages, and RPE are similar on OCT. Therefore, it is highly desirable to develop a novel method, such as OCTA, for monitoring nAMD. OCTA can simultaneously provide functional (OCT angiograms) and morphological (OCT B-scans) information and may be performed monthly because it is simple, quick, and non-invasive[15].

Current study aimed to assess the ability of the OCTA technique in detecting active CNV and to determine efficacy (sensitivity and specificity) of SS-OCTA. In our study OCTA has proved reliable in distinguishing between the two types of CNV: occult and classic, new blood vessels growing beneath or above the RPE, respectively.

During study we found a dark halo surrounding active CNV lesions and that was displayed as a hypointense clear zone on SS-OCTA images. This finding is consistent with Jiaet al[16] and Coscaset al.[17] who reported the same sign. An explanation for this dark halo is that CNV tends to develop a region of choriocapillaris alteration caused by impaired flow to compensate for ischemia. The region of choriocapillaris alteration is located underneath the CNV and extends beyond its margins in the form of a ring or halo and appears as hypointense or silent area on SS-OCTA images due to reduced blood flow[18].

In our study the sensitivity and specificity of OCTA in detecting the CNV secondary to nAMD was 85.1% and 80% respectively, almost same as that of Faridi A et al[19]. Four false negative eye with no decorrelation signal on en face OCTA due to sub-retinal haemorrhage. This finding is consistent with other studies, which have reported a decreased ability of OCTA to detect CNV in eyes with subretinal-haemorrhage. Moult et al[20] reported in their series that the single case in which OCTA revealed false-negative result had dense subretinalhemorrhage that caused severe attenuation of the SS-OCT signal. Faridiet al[19] concluded that sensitivity of en face

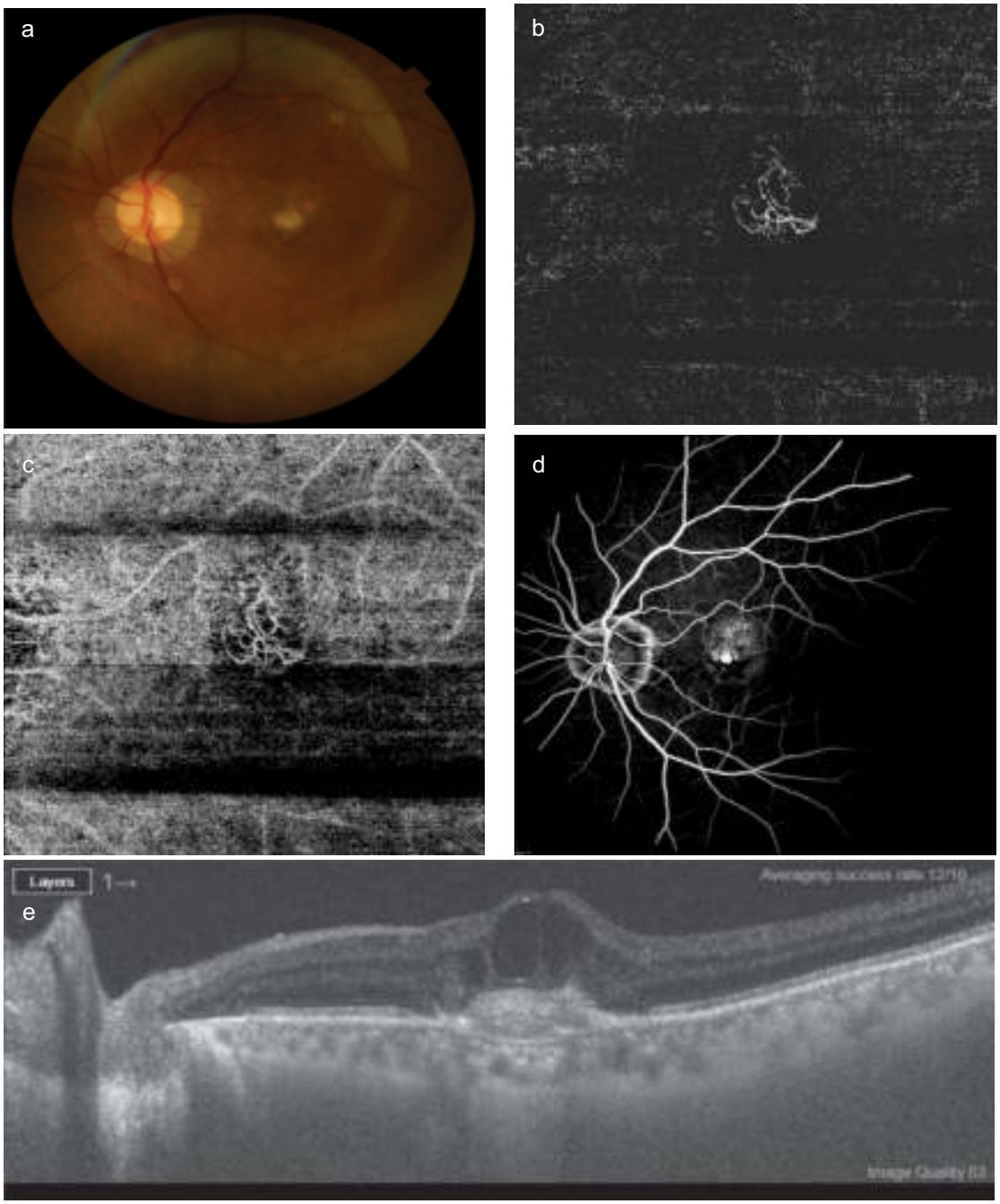

Figure 1.(Original)Multimodal imaging of a type II choroidal neovascularization (CNV), evaluated as a true positive case (a)Fundus of left eye showing yellow lesion at fovea .(b-c) A 6 × 6mm optical coherence tomography angiography slab at the outer retina and at the choriocapillaris showing a well-circumscribed branched CNV. (d) late frame fluorescein angiography displaying a small area of late leakage (white arrow) in the foveal area (e) OCT showing cystoid spaces and subretinal hyper-reflective material.

OCTA improved to 94% if eyes with subretinalhemorrhage were excluded. Jiaet al[16] demonstrated the ability of OCTA to detect and quantify CNV in 10 patients with wet AMD where OCTA provided better visualization of the neovascular network with respect to FA, as images were not obscured by subretinalhemorrhage or other artifacts. De Carlo et al[12] reported that the sensitivity and specificity of OCTA in detecting CNV secondary to wet AMD were 50% and 91%, respectively. Low sensitivity was due to small sample size and blockage from large amounts of retinal hemorrhage in some patients. Nikolopoulouet al[21] reported that the sensitivity and specificity of OCTA in detecting CNV

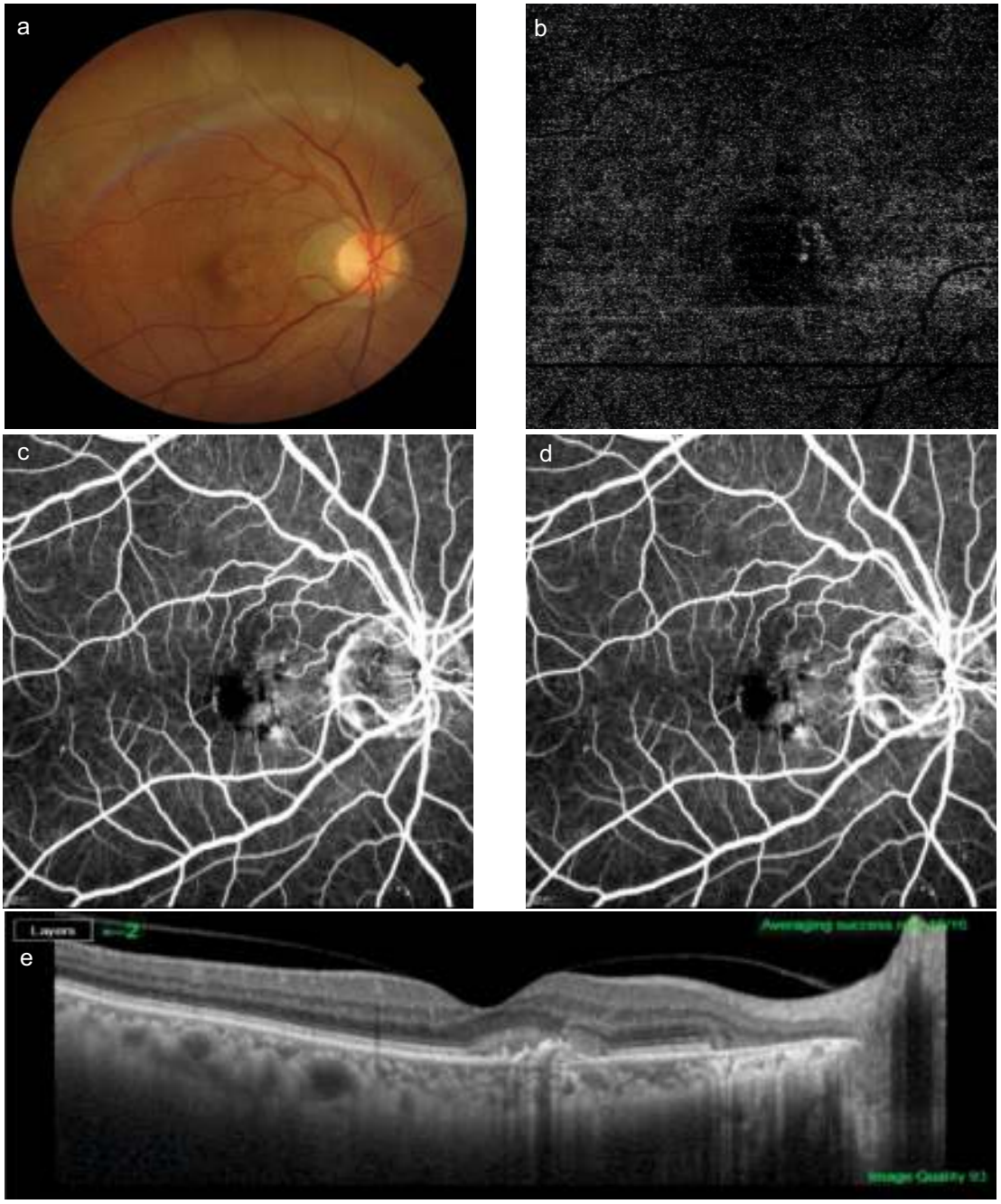

Figure 2: (Original)Images of choroidal neovascularization (CNV) observed in false-positive case on optical coherence tomography angiography (OCTA). (a) Fundus photo from a 62 -year-old man showing mild RPE irregularity (b) A 6∗6-mm En face optical coherence tomography angiogram of the outer retina showing a CNV in the juxtafoveal space (white arrow). (c and d) Early- and late-frame FA images of the patient displaying mild hyperfluorescence that is stable throughout the FA in the region of CNV without pooling. (e) Mild RPE irregularity seen on the spectral-domain optical coherence tomography corresponding to fundus picture.

secondary to wet AMD 88% & 90 % respectively.

In our study OCTA showed high sentivity in detecting type I CNV. This result was partially in discordance with Nikolopoulouet al[21] who stated that OCTA would display worse sensitivity in naïve CNV, due to undetectable flow inside the small peripheral branches of the neovascular complex.

In our study active CNV on OCTA showed well-defined complexes, dark halo around the lesion and numerous tiny anastomotic capillaries with thin walls and small diameter. There was excellent level of correlation in treatment decision based on OCTA compared to FFA. This result is consistent with findings of Coscaset al[17] and Spaideet al[22]. Coscaset

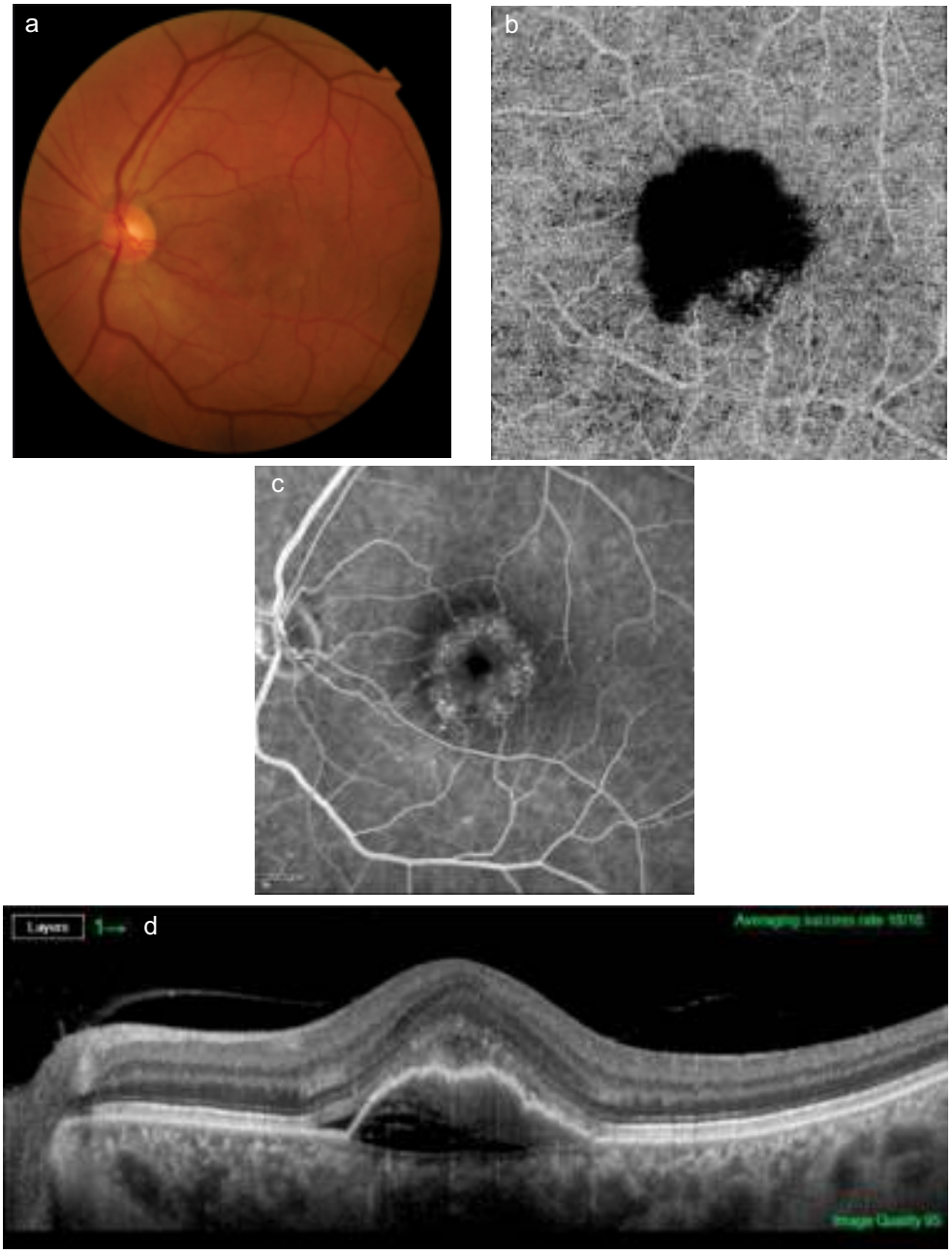

Figure 3: (Original)Images of subretinalhemorrhage observed in false-negative case on optical coherence tomography angiography (OCTA). (a)Color fundus photograph of the patient subretinalhemorrhage. (b) A 6∗6-mm En face angiogram of choriocapillaries not showing any CNV (c) Late-frame FA image displaying big leakage and pooling at the around the macula together with posterior pole pigment epithelium detachment. (d) Spectral-domain optical coherence tomography (SD-OCT) demonstrating subretinalhemorrhage with the retinal pigment epithelial (RPE) detachment.

al[17] had compared the OCTA with traditional multimodal imaging in patients with wet AMD and found that there was high inter-observer agreement both for treatment decision in conventional multimodal and for pattern I (active CV) or pattern II (inactive CNV) definition in OCTA imaging analysis.

SS-OCT can provide clues suggesting the presence of CNV, such as the presence of SRF, IRF, and subretinal hyper-reflective material, and allows identification of areas where the RPE is separated from BM.

In our study, the sensitivity of OCT along with en face OCTA in detecting the active CNV secondary to AMD compared to FFA was 85.1% and specificity was 80%. Our findings demonstrate that OCTA is able to detect the neovascular complex in most of the cases

of nAMD, allowing the analysis of the morphology of the CNV in every single patient.

CONCLUSION:

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

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