Retinal and Choroidal Imaging Update

Multimodal imaging of adult-onset foveomacular vitelliform dystrophy

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Abstract

Adult-onset foveomacular vitelliform dystrophy (AOFVD) is a clinically heterogeneous maculopathy that may mimic other conditions and be difficult to diagnose. It is characterized by late onset, slow progression and high variability in morphologic and functional alterations. Diagnostic evaluation should include careful ophthalmoscopy and imaging studies. The typical ophthalmoscopic findings are bilateral, asymmetric, foveal or perifoveal, yellow, solitary, round to oval elevated subretinal lesions, often with central pigmentation. The lesions characteristically demonstrate increased autofluorescence and hypofluorescent lesions surrounded by irregular annular hyperfluorescence on fluorescein angiography. Optical coherence tomography studies demonstrate homogenous or heterogeneous hyperreflective material between the retinal pigment epithelium and the neurosensory retina. The visual prognosis is generally favorable, but visual loss can occur from chorioretinal atrophy and choroidal neovascularization.

Keywords: Adult-onset foveomacular vitelliform dystrophy, Optical coherence tomography, Imaging, Macula, Pattern dystrophy

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Introduction

Adult-onset foveomacular vitelliform dystrophy (AOFVD) is a relatively uncommon macular disease first described by Gass in 1974. It generally presents in the fourth to sixth decades of life in patients who are visually asymptomatic or have mild blurring of vision, small central or paracentral scotomas, or mild metamorphopsia. It is often discovered incidentally on routine examinations. Generally, the visual loss is slowly progressive, but almost all patients retain reading vision in at least one eye throughout their lives.

AOFVD is a clinically heterogeneous disease displaying variability in the size, shape, pigmentary changes, and distribution of macular lesions. The typical patient has bilateral, asymmetric, foveal or perifoveal, yellow, solitary, round to oval elevated subretinal lesions, often with central pigmentation. The various descriptions in the literature do not make for an easy diagnostic approach, and this disease is often confused with other pigment epithelial alterations. Most often, AOFVD is misdiagnosed as age-related macular degeneration, but it can also mimic Best disease. When these patients are referred to a retina specialist for evaluation, few of them are suspected of having AOFVD.

It is therefore important to carefully define the ophthalmoscopic and imaging characteristics of this maculopathy to improve the diagnostic accuracy. This review will discuss different imaging modalities and associated findings that are characteristic of AOFVD.

Clinical examination findings

AOFVD is generally characterized by mild visual loss. In one study of 21 eyes, best-corrected visual acuity ranged from 20/25 to 20/400, with a mean visual acuity of 20/50.
eyes were better than 20/40 and 11 eyes were between 20/40 and 20/63. Only 4 eyes were worse than 20/63. Other studies showed similar distributions. Renner et al. found that 38 of 75 eyes had normal color testing. The other 37 eyes showed nonspecific errors of variable severity without any typical axis of confusion. Upon visual field testing, 28 of 53 eyes had normal visual fields, whereas 25 demonstrated a central scotoma. An absolute scotoma was observed in only four eyes.

On ophthalmoscopy, AOFVD is characterized by various patterns of unilateral or bilateral, yellow, round to oval elevated subretinal lesions, that often contain a central small, pigmented spot (Fig. 1). Lesions can be barely detectable or up to one disk area in size, are located at the fovea or the perifoveal region, and may be surrounded by small drusen. Bilateral lesions were present in 29 of 43 patients in one study and in 11 of 49 patients in another. Another evaluation of 8 patients with AOFVD revealed the presence of a central small, pigmented spot bilaterally in 6 of the 8 patients. In 2 eyes, there were several smaller yellow flecks close to the central lesion and the yellow material was found to fade gradually from the center of the lesion toward its periphery. Importantly, patients may also present later in the course of the disease when the lesions take on different clinical characteristics. Eventually, the lesions may fade, leaving an area of RPE alteration or atrophy.

Complications of the disease that can cause visual loss include choroidal neovascularization in up to one-third of patients, geographic atrophy, and outer retinal atrophy. Abrupt visual changes may occur as a result of new onset.

Figure 1. Adult-onset foveomacular vitelliform dystrophy in a 64-year-old man who presented with blurry vision, previously misdiagnosed as age-related macular degeneration. (A and B) Color fundus photographs show bilateral, vitelliform, circular, foveal lesions. (C and D) Infrared imaging shows central white spots surrounded by rings of darker material bordered by mottled outlines of white material. (E and F) The lesions have central hypoautofluorescence surrounded by a ring of hyperfluorescence. (G and H) Red free frames show the central white spots. Fluorescein angiography shows mottled foveal hyperfluorescence with late staining without leakage. (I: OD at 01:02, J: OS at 00:30, K: OD at 04:38, L: OS at 4:48). (M) Horizontal spectral-domain optical coherence tomography (SD-OCT) OD shows a disrupted external limiting membrane (ELM) and a mottled and hyperreflective photoreceptor layer that overlies a subretinal hyperreflective dome-shaped lesion. (N) Vertical SD-OCT scan of the left eye (right side of the image is superior macula), showing a mottled ELM and inner segment/outer segment junction, which overlies a heterogeneously hyperreflective subretinal material. The arrow points to an optically empty zone superiorly within the subretinal space, signifying a subtle pseudohypopyon.
choroidal neovascularization, which presents with the typical findings. On exam, there are no findings suggestive of chorioretinal inflammation, and there is no evidence of subretinal fluid or hemorrhage in the absence of choroidal neovascularization. Also, abnormalities outside of the macula are rare. AOFVD differs from vitelliform dystrophy or Best disease by many characteristics. The lesions in AOFVD are usually small, but when they are larger, they can mimic those seen in Best disease. AOFVD also has a later onset (40–70 years of age), presents with moderate symptoms, and has a normal or mildly subnormal electrooculogram (EOG). In Best disease, the onset is usually early (often before age of 30) and patients can maintain relatively good vision even with a large macular lesion throughout the course of the disease. Unlike AOFVD, Best disease is always associated with an abnormal EOG. Additionally, although most people with Best disease have a single foveal lesion, there are numerous reports of patients that have multiple vitelliform lesions.

Autofluorescence

The condition is characterized by increased autofluorescence within the foveal yellow lesion, reported in 76% of patients in one study. It has been previously established that autofluorescence is derived from lipofuscin in the retinal pigment epithelium (RPE). The high level of autofluorescence seen in AOFVD patients indicates an abnormal accumulation of lipofuscin, which is consistent with histologic studies (discussed later). (Fig. 1)

Fluorescein angiography

Fluorescein angiography (FA) demonstrates an early central hypofluorescent spot surrounded by an irregular ring of hyperfluorescence (Figs. 1 and 2). The central area of hypofluorescence corresponds with the yellow lesion seen clinically (whitish material seen on red free photographs). In the later frames, the lesion can persist as a hypofluorescent spot with no staining or show staining of variable intensity without leakage. One study showed 16 of 21 eyes with central staining in the late stages with the other 5 eyes demonstrating persistent hypofluorescence. The surrounding ring of hyperfluorescence often increases in intensity in later images. One study showed this phenomenon in 65 of 72 eyes. In contrast, there are reports of patients without the classic hypofluorescent spot and with only well-delineated central hyperfluorescence. Therefore, it is important to note the variability in FA findings.

Indocyanine green angiography

Indocyanine green angiography (ICG) in patients with AOFVD reveals no abnormality in choroidal perfusion. One study discussed the two main characteristic features: a central hypofluorescent spot, which was evident in the early frames up to the late phases, and an irregular, round hyperfluorescent ring surrounding the central spot. The central hypofluorescent spot blocked the underlying choroidal vessels and seemed to correlate well with the central pigmented spot noted on biomicroscopy. This central dark spot was interpreted as the consequence of the RPE clump that was described by Gass and Jaffe and Schatz in their histological analysis of AOFVD. In addition, there was no difference in ICG pattern between cases, even comparing patients with and without a central pigmented spot on clinical exam. Therefore, all patients may have this central pigmented clump, but in some patients the pigmented clump might be covered by the yellow material and thus, not visible on exam.

The hyperfluorescent ring surrounding the central hypofluorescent spot was visible on ICG after only a few minutes. It increased in intensity but not in size and it was detectable up to the late phase during the reduction of the background fluorescence due to the dye out-flow.

Optical coherence tomography

The exact location of the vitelliform material in AOFVD was not fully elucidated until the development of optical coherence tomography (OCT) imaging. Previous reports that subjectively analyzed color or monochromatic stereoscopic photos described the material as subretinal, sometimes
at the level of or under the RPE. However, not until the development of OCT was the location fully elucidated. OCT is a noninvasive technique that provides optical cross-sectional images of the retina and morphologic information similar to that obtained from histologic sections.

Using time-domain (first generation) OCT, Benhamou et al. suggested that the vitelliform material was located between the sensory retina and the RPE. In this study, 16 of 21 eyes showed the yellowish material as a highly reflective area located between the hyporeflective photoreceptor layer and the hyperreflective RPE. In most cases, the RPE was more reflective than the subretinal material. These eyes also showed late staining on FA without leakage. The other five eyes did not have late staining, and their OCTs showed the macular lesions as focal thickening of the RPE with no identifiable overlying hyperreflective material. In all cases with underlying hyperreflective material, the macula was raised by the material and showed overlying retinal thinning. In 20 eyes, there was a disappearance of the normal foveal depression from the subfoveal material or RPE thickening. All 21 eyes were without disappearance of the normal foveal depression from the subfoveal material or RPE thickening. All 21 eyes were without disappearance of a well-defined Verhoeff membrane.

The finding of five eyes without late staining on FA and no subretinal material, was explained by different stages of AOFVD and the differences in morphology that present at different stages. It has been shown that, with time, the subretinal material progresses slowly toward fragmentation and then disappears. The disappearance of this material is followed by the occurrence of atrophic RPE lesions and the appearance of pigmented spots.

Benhamou et al. confirmed these findings in a case report using third generation (3G) time-domain OCT, locating the vitelliform accumulation between the junction of the photoreceptor inner and outer segments (IS/OS interface) and the RPE/choriocapillaries complex. However, Pierro et al. had previously reported that the AOFVD lesions were located in the sub-RPE space, which created controversy as to the location of the lesions.

Further studies with improved imaging techniques confirmed the location of the deposits and resolved the previous confusion. Compared to time-domain OCT, spectral-domain OCT technology greatly improves the resolution and image acquisition speed. A recent spectral-domain OCT study evaluating the topographic features of AOFVD was consistent with Benhamou’s study and showed the vitelliform material as a highly reflective dome-shaped lesion located between the photoreceptor layer and the RPE. The subretinal material was shown to be homogenous in 14/60 eyes and heterogeneous in 36/60 eyes. This study also found OCT characteristics that included hyper-reflective clumps within the outer plexiform and outer nuclear layers in 28/60 eyes, a highly reflective photoreceptor IS/OS interface in 9/60 eyes, disappearance of a well-defined Verhoeff membrane (the optical layer between the RPE and the photoreceptor IS/OS interface) over the vitelliform lesion in 20/60 eyes, and irregularity to the RPE with hyperreflective motting in 14/60 eyes. These findings suggested the earliest alteration in the subretinal environment in AOFVD involves the layer between the RPE and IS/OS interface with the accumulation of vitelliform material. Interestingly, the RPE may demonstrate hypertrophy and sub-RPE deposits.

This same group had previously suggested a four-stage classification for AOFVD based on the one that was established for Best vitelliform macular dystrophy. These stages included vitelliform, pseudohypopyon, vitelliruptive and atrophic, in progressive order. The vitelliform stage is the classic dome-like lesion with subretinal vitelliform material. In the pseudohypopyon stage, the vitelliform material settles inferiorly within the subretinal space, to create an optically empty zone superiorly, with hyperreflective material inferiorly, and a horizontal demarcation at the interface. The vitelliruptive stage is characterized by collapse of the dome-like shape into a lesion with heterogeneous vitelliform material and hyperreflective clumps within the inner retina. Finally, spectral domain OCT is also able to visualize choroidal atrophy, characterized by loss of the outer retina and varying degrees of thinning/mottling and loss of the RPE and choriocapillaris. This would suggest the final atrophic stage.

Pierro et al. showed a correlation between the thinning of the neurosensory retina over the vitelliform lesion and poor visual acuity (P = 0.001). Visual acuity was also found to worsen in eyes that progressed through the four stages discussed above, in eyes with disruption in the IS/OS interface, and in those with changes in lesion reflectivity on spectral-domain OCT (P = 0.03). Also, as eyes progressed from one stage to the next on the continuum, mean central macular thickness (P = 0.004), maximal thickness of the lesion (P = 0.001), and maximal width of the lesion showed significant changes (P = 0.04).

Querques et al. also previously correlated OCT findings in patients with AOFVD with the extent of visual function impairment using microperimetry, a relatively new psychophysical method that makes it possible to compare retinal morphologic features with retinal function by simultaneously testing central retinal sensitivity and fixation patterns in relation to the fundus image. The study found that reduced thickness of the neurosensory retina at the foveola and reduced visual acuity were correlated with advanced stage of the disease (P = 0.001 and P = 0.0062, respectively). Moreover, worse visual acuity correlated with reduced thickness of the foveal neurosensory retina (P = 0.02), was associated with the development of an absolute scotoma (P = 0.03), eccentric fixation (P = 0.01), and unstable fixation (P = 0.03).

In comparing AOFVD to Best disease, reports showed that Best disease is more often being associated with serous neurosensory detachments on OCT. A recent study compared patients with AOFVD to those with age-related macular degeneration (AMD) using spectral domain OCT. Macular choroidal thickness in 38 patients with AOFVD, neovascular AMD or nonneovascular AMD was evaluated using enhanced depth imaging optical coherence tomography (EDI-OCT). Subfoveal choroidal thickness in AOFVD patients with subretinal fluid significantly increased (P = 0.001) compared with that of neovascular AMD and nonneovascular AMD, as well as that of normal controls (P = 0.001). This finding was interesting since choroidal thinning is usually observed in advanced AMD. Therefore, choroidal thickness may be a measurement to help differentiate between AMD and AOFVD.

Electrophysiologic studies

Electrophysiologic testing, both electrooculography (EOG) and electoretinography (ERG), is typically within nor-
mal limits in patients with AOFVD. The EOGs of eyes with AOFVD tend to be normal but can also be mildly subnormal, whereas the EOG in Best disease patients is always abnormal.

Renner et al. evaluated 21 eyes with AOFVD using EOG. A normal light increase (≥ 160%) was present in 6 patients in both eyes and in 3 patients in one eye. A slightly reduced light increase (149–155%) was observed in 2 patients in both eyes and in two other patients in one eye. Patients with a definite yellow macular lesion were more likely to have the subnormal EOG response.

Additionally, a full field ERG was recorded in 43 eyes. The b-wave amplitude of the maximum cone response was slightly reduced in 12 eyes, as was the single flash cone response in 18 eyes. The 30-Hz flicker response was reduced in the majority of eyes (31 eyes, 72%) Most prior studies, however, reported normal ERGs in patients with AOFVD.

**Histopathology**

A number of clinicopathologic studies in eyes with AOFVD have shown massive accumulation of lipofuscin pigments within the RPE in the macula. Evidence of RPE and photoreceptor loss, as well as infiltration of these layers with lipofuscin pigment containing macrophages have also been described.

Patinelly et al. performed detailed pathologic studies of two postmortem eyes from a 61 year old woman with AOFVD. The findings were most significant for abnormalities found within the RPE and photoreceptor layers. By light microscopy, marked focal atrophy of the pigment epithelial cells in the foveolar area was bordered by hypertrophic RPE. Interpose between the atrophic RPE and Bruch’s membrane was a scattered eosinophilic, fusiform collagenous plaques. The sensory retina overlying the deranged RPE displayed marked atrophy of the outer nuclear layer with loss of photoreceptor inner and outer segments. Lipofuscin pigment-laden macrophages containing periodic acid-Schiff-positive material had migrated into the atrophic, outer sensory retina. Ultraviolet fluorescent microscopy demonstrated massive accumulation of lipofuscin pigment within the macular RPE as well as within macrophages in the atrophic outer retina. By scanning electron microscopy, a confluent area of flattened, atrophic retinal pigment epithelial cells was rimmed by taller, hypertrophic RPE cells. By transmission electron microscopy, the pigment epithelial cells contained myriad lipofuscin granules. Bruch’s membrane and the intercapillary pillars were slightly thickened and the choriocapillaris was patent.

Several genes have been associated with AOFVD. First, BEST1 mutations are most commonly associated with Best vitelliform macular dystrophy, but the gene has been implicated in a broad spectrum of ocular phenotypes. BEST1 mutations account for approximately half of Best vitelliform macular dystrophy cases. The bestrophin 1 protein, expressed in the RPE, is a chloride channel involved in intracellular calcium signaling.

Mutations in this gene have also been associated with AOFVD in up to 25% of patients. Second, PRPH2/RDS was identified in 1991 and has also been associated with a variety of macular dystrophies, cone and rod dystrophies, and retinitis pigmentosa. The RDS-Peripherin protein is expressed in rod and cone photoreceptors and plays a pivotal role in the formation and stability of disks forming a heterodimer in rods and rod outer segment protein. Over 90 different mutations in this gene have been reported and approximately 20 of them have been associated with AOFVD, accounting for a small percentage of cases (2–18% of patients). In a study searching for mutations in the BEST1 gene and PRPH2 gene in 19 patients with AOFVD, 2/19 (10.5%) of the cases had a PRPH2 mutation, and none carried a BEST1 mutation. The 2 patients found to have PRPH2 mutations had family histories of AOFVD. However, there were three other patients with family histories of AOFVD where mutations were not identified.

Renner et al. examined the DNA samples of 21 patients for mutations in BEST1 (n = 11) or PRPH2/RDS (n = 10). A disease-associated sequence alteration was detected in only one patient, however. This patient carried a 17 base pair deletion in exon 2 (609_625del17) of the PRPH2/RDS. The mutation results in a frameshift in codon 203 (Arg203fs) and leads to premature translation termination eight codons downstream. This patient had central yellow lesions in both eyes. Several other reports have also shown that AOFVD can be associated with mutations in PRPH2/RDS.

Because of a highly variable penetrance and expressivity and the controversy on mechanism of inheritance (sporadic versus autosomal dominant), there is difficulty with genetic counseling. However, family members can generally be reassured given the good visual prognosis in the majority of patients.

**Conclusion**

In summary, AOFVD is characterized by late onset, slow progression and high variability in morphologic and functional alterations. The diagnostic evaluation should include careful ophthalmoscopy and imaging studies. Imaging of AOFVD characteristically shows a lesion with increased autofluorescence, central hypofluorescence with a surrounding irregular hyperfluorescent ring on fluorescein angiogram, and a nonfluorescent spot with surrounding irregular, round hyperfluorescence on ICG. Spectral domain OCT shows accumulation of hyporeflective material between the neurosensory retina and the RPE, and is also capable of demonstrating other findings such as focal chorioretinal atrophy. AOFVD is a potentially difficult diagnosis to make, but multimodal imaging with the aforementioned modalities will aid in the differentiation of this maculopathy from other conditions.
Conflict of interest

There is no conflict of interest to declare.

References


