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REVIEWS

Quantification of inflammation in inflammatory eye diseases

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Abstract

Measuring the cells and flare present in the anterior chamber and vitreous humor is a universally accepted method for quantifying inflammation in inflammatory eye diseases. However, one of the major disadvantages of this method is subjective grading. This can be overcome by measuring the cells and flare by laser flaremetry. But it is not widely available. The current review highlights the different methods and various parameters used clinically to assess the inflammation and the role of various imaging techniques in the diagnosis and monitoring of the response to treatment in ocular inflammatory diseases.

Introduction

Eye is a unique organ, which can be visualized through direct examination for real time pathological or inflammatory changes. Moreover, non-invasive imaging modalities like ultrasound and other modalities can assist in accessing the areas that cannot be visualized directly. The changes can be quantified in different ocular inflammations and these conditions are categorized based on layers involved such as uveitis (uveal tract), scleritis (sclera), reitinitis (retina), and vitritis (vitreous humor). They are further characterized by findings as granulomatous, non-granulomatous (depending on the probable pathological characteristics), and as acute and chronic inflammations based on the duration of disease. The greatest advantage in eye is majority of the inflamed areas can be visualized by direct examination.

Damage to an organ in inflammatory conditions depends on the quantity and type of inflammation (proportional to the total duration of inflammation). While prescribing immune suppressants, either systemic or topical, a conscious decision on the quantum of immune suppression and the duration of therapy will be based on the approximated estimation of inflammation. Thus, quantifying inflammation essentially guides the clinician in deciding the treatment strategy and duration. The present review focuses on different methods used for assessing ocular inflammatory disease activity, which assist in the management of eyes with varied inflammatory conditions.

Uveitis

In patients with uveitis, presence of various clinical indicators can give clues to the possible etiology, chronicity, and severity of the disease. Meticulous ocular examination using a slit lamp and indirect ophthalmoscopy along with modern imaging techniques can grade or quantify severity of the inflammation.

Clinical features of uveitis

Ocular signs of a systemic inflammatory disease may be reflected in all ocular structures including the eyelids and the optic nerve, and they aid clinicians in differentiating granulomatous and non-granulomatous inflammations. Presence of poliosis or vitiligo on eyelids may indicate Vogt-Koyanagi-Harada disease (VKH), conjunctival granulomas (millet-seed sign) may suggest sarcoidosis, and corneal endothelium may show keratic precipitates. Increase in vascular permeability and disruption of blood aqueous barrier due to inflammation causes flare in the anterior chamber and chemotaxis. This is responsible for the presence of inflammatory cells in the anterior chamber and vitreous reaction. These cells can be clinically graded and quantified.

Standardized nomenclatures have been employed to standardize the uniformity in reporting the gradation of clinical findings. Most commonly used nomenclatures were developed by the Standardization of Uveitis Nomenclature (SUN) working group for grading inflammation in anterior and vitreous chambers.[1] Observer can assess cells and

flare in the anterior chamber using a slit lamp beam of 1 X 1 mm in height and width, when thrown at an angle of 45-60°. Based on the finding, the inflammation can be categorized from 0 to 4+ grade (Table 1 and 2).

Although a standard system assists in translating the findings, its major disadvantages are subjective nature and limited reproducibility.

Other indicators of inflammation that are not included in grading and not scored separately in the present system are: nodules, vascularization of iris or angle, trabeculitis, anterior and posterior synechiae, atrophy of iris, and heterochromia. The inflammation occurring in intermediate segment of the eye, which leads to vitritis, is graded depending upon the number of vitreous cells and haze according to the following National Institutes of Health (NIH) classification (Table 3 and 4).[2]

The findings like vitreous exudates in the form of snow balls provide clue about the chronicity of the disease. Larger snow ball may indicate granulomatous nature of the inflammation. Chronic intermediate uveitis can also cause cyclitic membrane formation and secondary ciliary body detachment, leading to hypotony or prephthisical stage. Unfortunately these signs cannot be clinically assessed or graded.

Posterior segment inflammation can lead to cystoid macular edema, retinal or choroidal infiltrates, inflammatory sheathing of vessels, exudative, tractional or rhegmatgenous retinal detachment, retinal pigment epithelium (RPE) hypertrophy or atrophy, edema, and secondary atrophy of retina, choroid, and optic nerve.

Table 1: The SUN working group grading system for anterior chamber cells

Grade	Cells in field
0	<1
0.5+	1-5
1+	6-15
2+	16-25
3+	26-50
4+	>50

Table 2: The SUN working group grading system for anterior chamber flare

Grade	Description
0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plastic aqueous)

Table 3: NIH grading system for vitreous cells

Grade	Number of vitreous cells
0	No cells
0.5+	1-10
1+	11-20
2+	20-30
3+	30-100
4+	>100

The sequelae can also include preretinal/subretinal fibrosis and choroidal neovascularization. These changes are currently considered to be inconsistent to grade the inflammation. Imaging for vasculitis, cystoid macular edema or chorioretinal infiltration may help in documenting improvement or worsening of inflammation.

Scleritis and sclerouveitis

Various autoimmune diseases are associated with the involvement of the sclera or cornea, or variable degrees of intraocular inflammation. McClusky scleritis scoring system has put forth guidelines for appropriate treatment of various grades of scleritis (Table 5a and 5b).[3] But a system of classification that considers the corneal and intraocular involvement, and prognosticates various stages of disease is lacking.

Though the system takes into account clinical features such as the inflammatory area, pain, and associated anterior chamber inflammation; it does not specifically address the corneal involvement and degree/severity of inflammation. It is more useful in following the disease course than assessing the severity of inflammation at a single visit. To overcome the above limitations, another system was proposed by Sen *et al.* based on photographic standards for grading the severity of inflammation. Severity of scleritis is graded from 0-4+ based on standard photographs after instillation of 10% phenylephrine for 15-20 minutes (Table 6). The researchers noted that the system aided in achieving good inter-observer agreement during the grading of scleritis among various examiners and suggested it as an easily applicable method for grading of severity.

Ancillary investigations

In addition to clinical observation, ancillary investigations can provide diagnostic clues and also help in monitoring response to treatment. Some of the major investigations that may aid in assessing inflammatory disease process are described below.

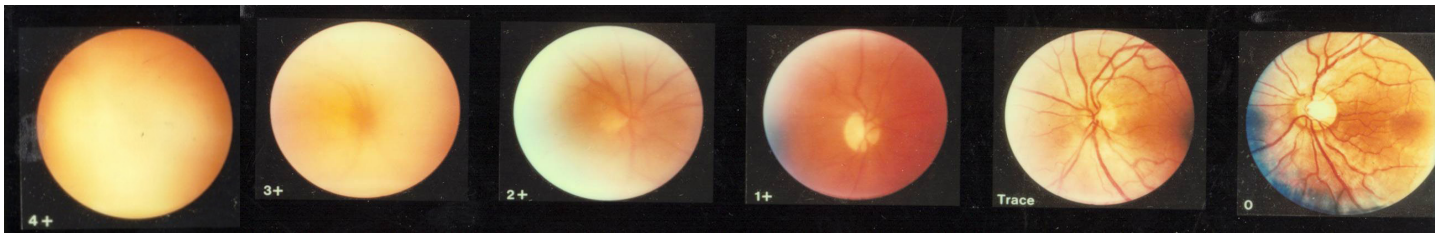
Laser flare photometry

Laser flare/cell photometer (LFP) comprises of a photomultiplier-photodetector for detecting back-scattered light reflected off from proteins and cells in the anterior chamber (flare). This is a more objective, quantitative method of measurement of intraocular inflammation and hence considered superior to slit lamp grading systems in diagnosing subclinical inflammation. It is also effective in monitoring treatment response and detecting disease relapses.[5] Gonzales *et al.* have reported an inverse relationship between LFP flare and visual acuity in patients with uveitis. A strong correlation was also found between LFP flare and complications such as posterior synechiae and macular edema, while no relationship was found between complications and anterior chamber cell or flare scores at the slit-lamp.[6]

Table 4: NIH grading system for vitreous haze (Fig.1)

Grade	Amount of vitreous flare/haze
0	No flare
0.5+	Trace
1+	Clear optic disc and vessels, hazy nerve fiber layer
2+	Hazy optic disc and vessels
3+	Optic disc visible
4+	Optic disc not visible

Fig. 1: Grading of vitreous haze



Source: Nussenblatt RB et al. Ophthalmology.1985;92:467-71.

Table 5a: McClusky scleritis scoring system

Parameter	Category	Score
Laterality	Unilateral	1
	Bilateral	3
Tenderness		0-4
Nodules	Single	2
	Multiple	4
Vision loss	< 2 lines	1
Scleral necrosis	Absent	0
	Present	2
Anterior chamber reaction	Grade 0-4	0-4
Intraocular pressure (IOP) >22 mm Hg		1
Vitreous cells	Grade 0-4	0-4
Retinal detachment present		4

Table 5b: McClusky scleritis scoring system (score-based treatment)

Parameter	Category
Mild (score < 9)	Oral/pulsed steroids
Moderate (score 9-12)	Azathioprine
Severe (score >13)	Intravenous methyl prednisololone (IVMP), cyclophosphamide, cyclosporine
Improvement	Score < by 2
Resolution	Score < by 4

Normal values for aqueous flare intensity have been found to be in the range of 2.9–3.9 ph/ms in healthy individuals between 20 and 40 years of age. Flare values have been found to increase slightly with age, reaching 5.0–6.5 ph/ms between 70 and 80 years. This increase could be due to the breakdown of the blood–aqueous barrier, changes in protein composition of the aqueous humor or cataract development.[7-9]

LFP has proven to be a guide to initiate and monitor treatment, and to detect relapses in patients with uveitis. In a study of 44 patients presented with acute episode of HLA B27 associated anterior uveitis, mean initial flare reported was 160 ± 22 ph/ms (range: 11–787 ph/ms). The corresponding decrease in flare noted after treatment with a standard therapeutic regimen for 2 and 8 days were 50 and 90%. In 15 out of the 44 patients enrolled, an additional periocular corticosteroid injection was needed because of insufficient decrease (less than 30% of initial flare) or increase in flare after 48 hrs. A flare level under 8 ph/ms was accepted as the resolution (end of an episode).[10] Hence meticulous adjustment of therapy in patients with HLA-B27-associated uveitis can be made with the help of LFP. Similarly, LFP is useful in monitoring response to treatment and titrating the treatment in diseases like Behcet's disease, VKH disease, Fuchs' uveitis, and uveitis associated with juvenile idiopathic arthiritis (JIA).[11-18] This method, though useful, is not universally available and hence one may have to rely on clinical grading.

Ultrasound biomicroscopy (UBM)

UBM is a high frequency (35-100 MHz) ultrasound used to assess inflammation in anterior segment of the eye. It is useful to study hidden structures such as ciliary body, ciliary angle, artificial lens haptic position, peripheral choroid, and pars plana, which are difficult to be visualized by direct

Table 6: Scleritis grading (following 10% phenylephrine application)

Score	Grade	Clinical description
0	None	Complete blanching after 10% PE
+0.5	Minimal	Localized pink appearance of the sclera around minimally dilated deep episcleral vessels
+ 1	Mild	Diffuse pink appearance of the sclera around mildly dilated deep episcleral vessels
+2	Moderate	Purplish pink appearance of the sclera with significantly tortuous and engorged deep episcleral vessels
+3	Severe	Diffuse redness of the sclera, the details of superficial and deep episcleral vessels cannot be observed
+4	Necrotizing	Diffuse redness of the sclera with sclera thinning and uveal show

examination. It is also useful to measure anterior sclera thickness. It can be used to study anatomical integrity of anterior segment (iris and lens) when cornea is opaque.

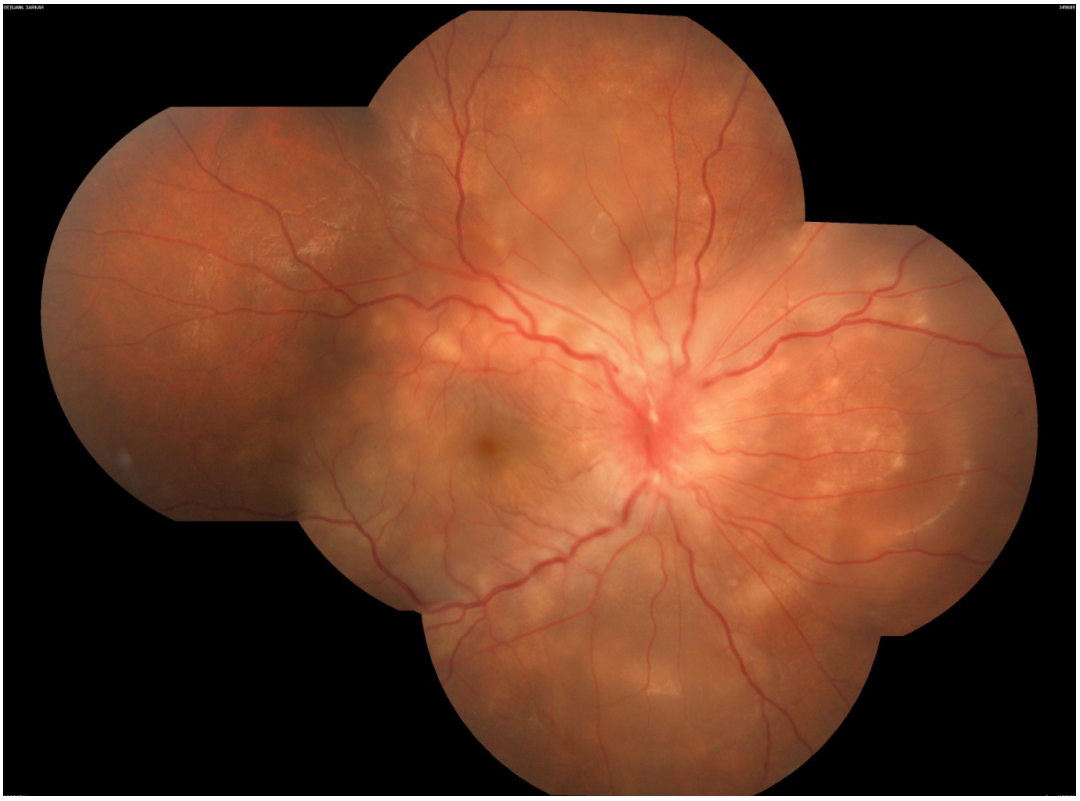
Fundus photography

Fundus pictures taken serially are useful to monitor treatment response for retinitis, choroiditis, vasculitis, and other inflammatory changes. Stereoscopic pictures are more useful to document macular edema, optic nerve head edema, choroidal neovascular membrane (CNVM), exudative retinal detachment (Fig. 2), and large choroidal granuloma. These are used to document response to treatment and monitor media clarity in patients with vitritis. Wide field retinal imaging is used to document the peripheral retinal changes in uveitis.

Ultrasonography (B scan)

Ultrasound has an important role in the evaluation of

Fig 2: Montage color fundus photograph of the right eye showing hyperemic disc with multiple serous retinal detachment in a case of VKH disease



uveitic conditions, especially if the media haze precludes adequate visualization of posterior segment. The features of posterior uveitis that can be documented on B scan are: vitritis, exudative membranes in the vitreous, posterior vitreous detachment (PVD), subretinal exudates or mass lesions, retinochoroidal layer or posterior scleral thickening, severe macular edema with detachment, exudative, tractional or rhegmatogenous retinal detachment, and choroidal detachment. In certain cases, it can also help in differentiating exudative retinal detachment (inflammatory) from rhegmatogenous retinal detachment (non-inflammatory).

In patients with anterior scleritis, the clinical signs such as episcleral and scleral congestion, and tenderness of sclera are remarkable. But in posterior scleritis, especially with no or minimal anterior segment findings, the diagnosis and assessment can be made only by ultrasound in the presence of features like diffuse/nodular retinochoroidal thickening, episcleral infiltration/edema, distension of Subtenon's space causing the 'T' sign and associated choroidal, ciliary body or exudative retinal detachments.

In a patient with complete PVD, dot echoes in subvitreal space may signify active inflammation. Inflammatory conditions of choroid like VKH, sympathetic ophthalmia, uveal effusion syndrome and masquerades like uveal lymphoid infiltration are associated with diffuse choroidal thickening, serous retinal detachment and vitritis that can be monitored on serial ultrasounds after treatment.

Quantification of the inflammation is possible in case of posterior scleritis by measuring thickness of posterior sclera and vitreous inflammation can be graded as mild, moderate, and severe.

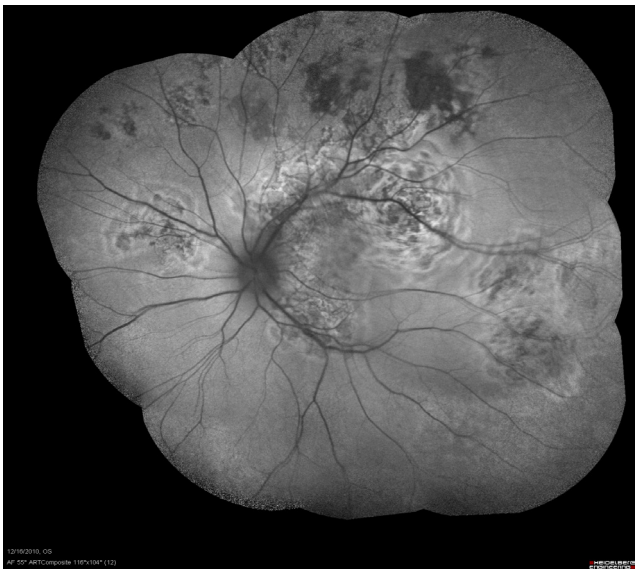
Autofluorescence

Fundus autofluorescence (FAF) is a rapid non-contact, non-invasive method to evaluate RPE function. The byproducts of RPE phagocytosis of photoreceptor outer segments consist of retinoids, fatty acids, proteins, and lipofuscin. Lipofuscin in turn accumulates and causes autofluorescence, hence this is a measure of metabolic activity of RPE cells. In inflammatory conditions, the metabolism of RPE cells is altered and hence autofluoresence is also varied depending upon the disease activity.

In fundus autofluorescence, areas of hyperautofluorescence suggest active inflammation and hypoautofluorescence indicate early activity, inactive or healed lesions. Mixed autofluorescence (hypo with hyper autofluorescence) suggest healing inflammation.[19]

Gupta *et al.* have reported four stages of disease activity in serpiginous-like choroiditis based on autofluorescence.

Fig. 3: Montage autofluorescence imaging of serpiginous-like choroiditis showing areas of hyperautofluorescence corresponding to the areas of active choroiditis with hypoautofluorescence lesions suggestive of healed lesions



Stage 1: lesions with active edge show an area of hyperautofluorescence at the borders of the active edge. As the disease starts healing, the hyperautofluorescence is replaced with hypoautofluorescence; Stage 2: disease shows healing lesions with mixed autofluorescence that are predominantly hyperautofluorescent; Stage 3: the lesions that are now progressively healing show mixed autofluorescence and are predominantly hypofluorescent (Fig. 3); and Stage 4: as the lesions become totally healed with scar, they show total hypofluorescence.[20]

Vasconcelos-Santos *et al.* described the FAF features of VKH. They found areas of hypoautoflurescence that corresponded to areas of peripapillary atrophy and atrophic scars, signifying atrophy of RPE and outer retina. The pigmented scars with thickening of RPE or Bruch's membrane layer were also found to be hypoautofluorescent. Clinically normal looking retina was found to be hyperautofluorescent, signifying subclinical inflammation. Hyperautofluorescence was also seen in areas of cystoid macular edema. Sunset glow fundus, disciform scars, and sectoral chorioretinal atrophic areas showed similar autoflouresencence as the background.[21]

Wide field fundus autofluorescence can be used to detect peripheral changes that are missed during routine fundus imaging.

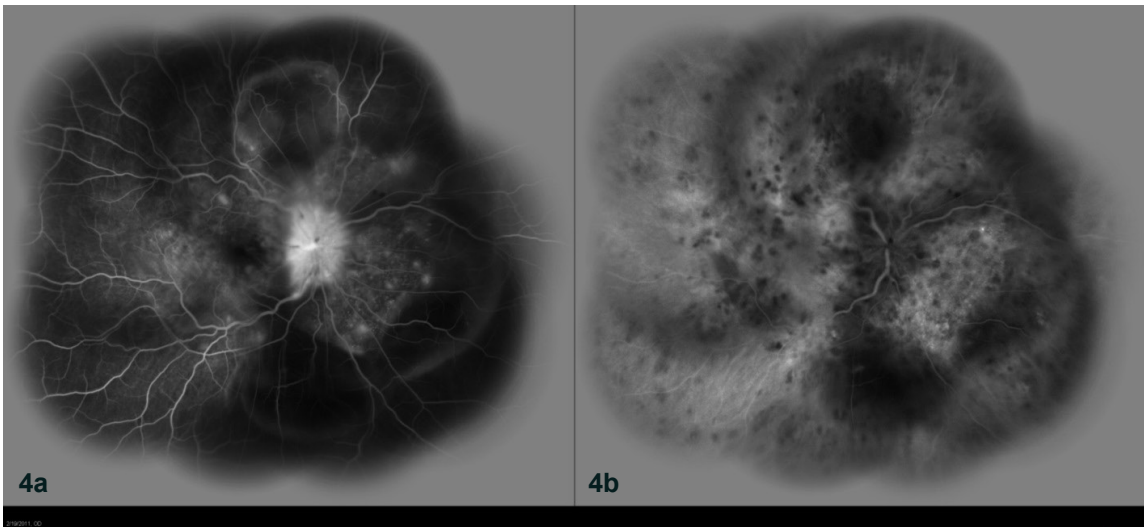
Fundus fluorescein angiography (FFA)

FFA is useful in identifying vascular leaks in patients with vasculitis and distinguishing active from inactive disease, which is important for monitoring treatment responses and chances for relapse. It also detects subclinical retinal capillary involvement that can be missed on clinical examination. Moreover, associated conditions like cystoid macular edema (CME), choroidal neovascular membrane (CNVM), vascular occlusions, areas of capillary non-perfusion and neovascularization can be better detected and studied with the help of FFA. Previously, CME was graded on the basis of FFA. Miyake classified CME as: Grade 0: no sign of fluorescein leakage; Grade I: slight fluorescein leakage into cystic spaces but not enough to enclose the entire fovea centralis; Grade II: complete circular accumulation of the fluorescein in the cystic space but its diameter is smaller than 2 mm; and Grade III: the circular accumulation of fluorescein is larger than 2.0 mm in diameter.[22]

The slightly modified classification for CME put forth by Yannuzzi is as follows: Grade 0: no perifoveal hyperfluorescence; Grade 1: incomplete perifoveal hyperfluorescence; Grade 2: mild 360 degree hyperfluorescence; Grade 3: moderate hyperfluorescent area being approximately 1 disc diameter across; and Grade 4: severe 360° hyperfluorescence with the hyperfluorescent area being approximately 1.5 disc diameter across.[23]

OCT has by and large replaced FFA as the investigation of choice for macular edema. According to MUST trial

Fig. 4a: Combined FFA and ICG imaging showing disc hyperfluorescence with multiple pinpoint hyperfluorescence with late pooling of the eye in FFA. Fig. 4b: Multiple hypofluorescence with staining and leakage of the choroidal vessels in the right eye in a case of VKH disease.



Research group, OCT was able to diagnose edema in 90.4% of cases compared to FA that gave useful information only in 77%. Nevertheless, FFA is a useful adjunct to OCT in cases where macular leakage is the determining factor for treatment.[24]

Though FFA is not the investigation of choice for choroidal diseases, certain features on FFA like initial hypofluorescent dots or areas of delayed choroidal filling with late pooling of dye in subretinal space with disc hyperfluorescence characterize VKH and sympathetic ophthalmia (Fig. 4a).

Indocyanine green angiography (ICGA)

ICGA is considered as an investigation of choice for choroidal pathologies, since it doesn't leak from choroidal vessels due to its larger size than fluorescein. Choroidal inflammation has been classified based on ICG as 1. Inflammation of choriocapillaris (choriocapillaritis) e.g. diseases like multiple evanescent white dot syndromes (MEWDS), acute posterior multifocal placoid pigment epitheliopathy (APMPPE), multifocal choroiditis, serpiginous choroiditis (predominantly affect choriocapillaris) and 2. Inflammation of choroidal stroma-stromal choroiditis in diseases like VKH, sympathetic ophthalmia, and birdshot chorioretinopathy.

ICGA can detect lesions that are not apparent, even on FFA. It can show hypofluorescence or hyperfluorescence. Choroidal stromal infiltration or choriocapillaris nonperfusion

Fig. 5a: Optical coherence tomography horizontal line scan image revealing posterior vitreous detachment with hyporeflective cystic space suggestive of cystoids macular edema with central retinal thickness of 496 microns in the right eye

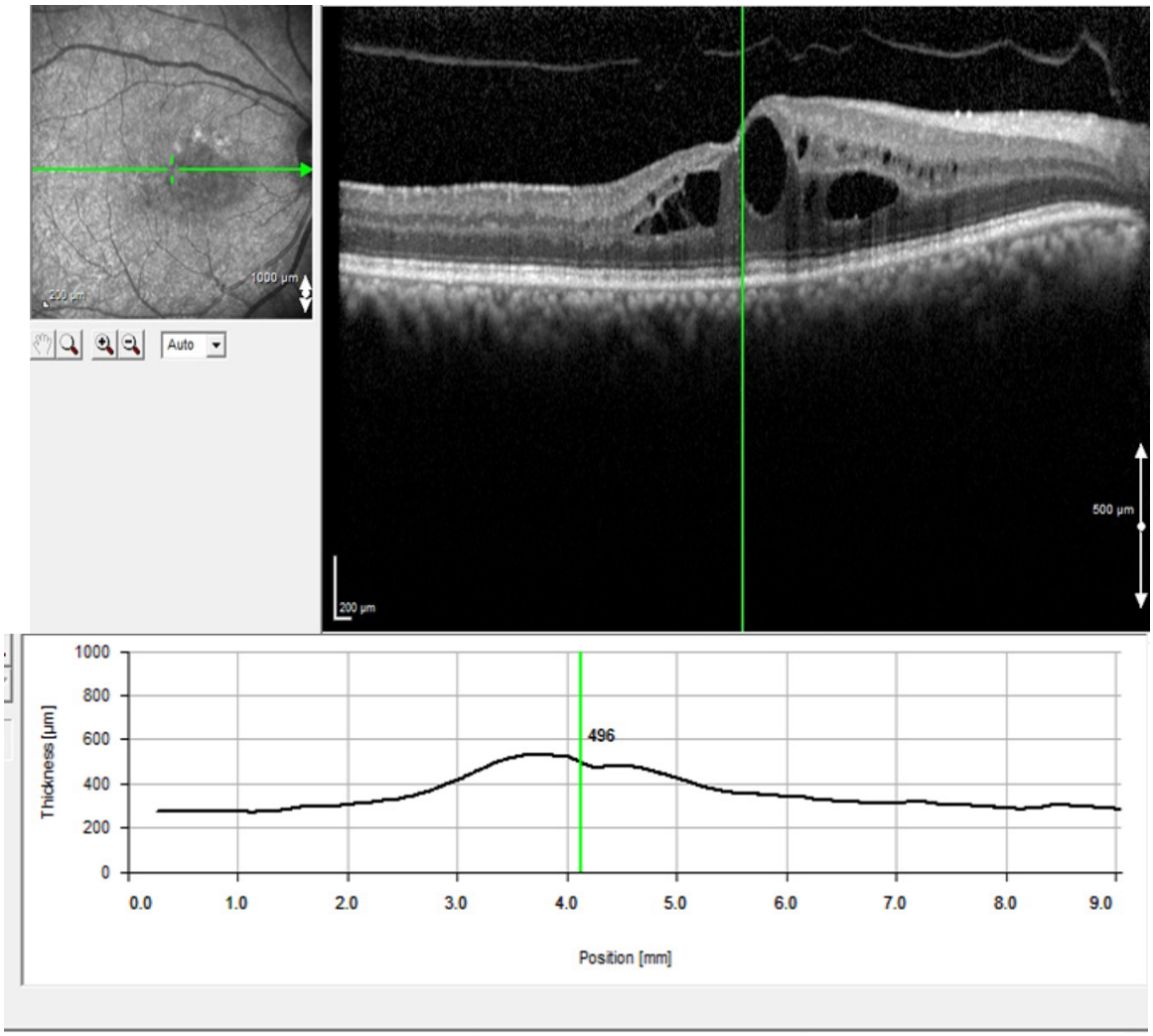
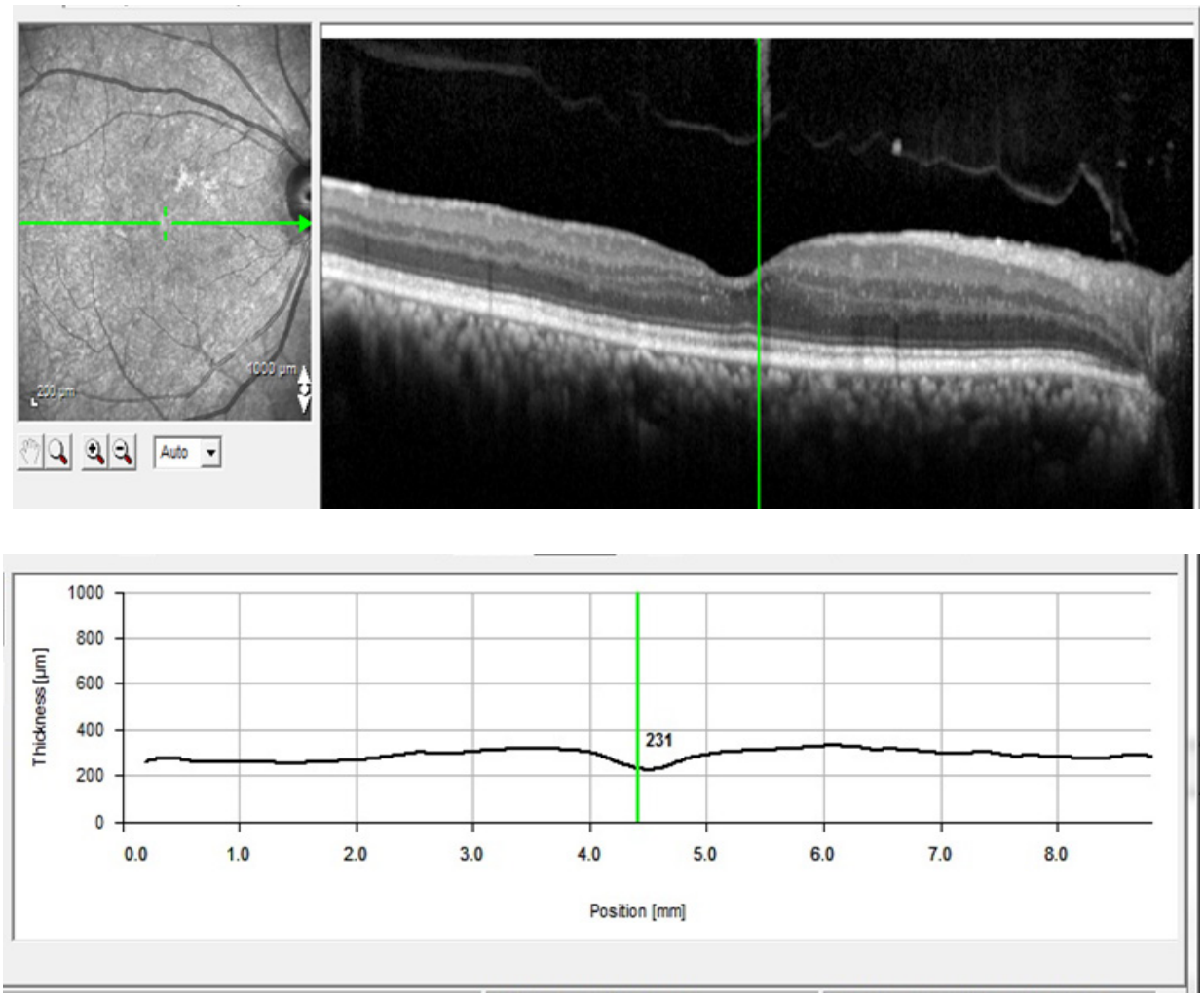


Fig. 5b: Horizontal line scan image of the right eye showing resolved cystoid macular edema with central retinal thickness of 231 microns



can lead to hypofluorescence with diffuse choroidal fluorescence in late phases (Fig. 4b). Hyperfluorescence can be caused by leakage from large inflamed choroidal vessels or late hyperfluorescent pin point leaks, signifying granulomatous disease.

Optical coherence tomography (OCT)

OCT is a useful tool for detecting inflammation and defining the location, extent, and depth of a lesion. It can document anterior segment changes to differentiate between episcleritis and scleritis in the posterior segment to detect the posterior vitreous cells and macular edema. This can be quantified and monitored after treatment. The imaging can also be used for detecting and monitoring associated features like vitreomacular traction (VMT), epiretinal membranes (ERM), and serous detachments of retina (especially in VKH and sympathetic ophthalmia).

Previously OCT could show only lesions closer to the vitreoretinal interface with greatest clarity due to the placement of focus at that interface. Combined depth imaging with focus both at choroidal and vitreoretinal surface have enabled better delineation and study of lesions placed anywhere in the retina or choroid.[25] This modality can measure central foveal thickness in micrometers, which may assist in quantifying and monitoring inflammation (Fig. 5a and 5b).

Cytokine estimation

Cytokines can be measured from the tears and ocular fluids in various uveitis entities.[26-29] IL-17 plays a major role in immune-mediated uveitis.[26] Yoshimura has showed that IL-6 is elevated in the vitreous fluid of patients with chronic uveitis.[27] IFN-ɣ is produced both in the eye and the peripheral blood of non infectious uveitis and it is increased

in the eye in cases of infectious uveitis.[28]

Conclusion

There are numerous pointers to inflammatory disease processes in the eye that can be detected clinically or with the help of investigations. A reproducible and universally acceptable system of grading of inflammation based on various clinical features and findings on imaging studies is highly essential for early diagnosis, appropriate treatment, titration of treatment, monitoring the disease, and early detection of relapses.

Competing interests
The authors declare that they have no competing interests.

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