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A review of the role of ultrasound biomicroscopy in glaucoma associated with rare diseases of the anterior segment

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Abstract: Ultrasound biomicroscopy is a non-invasive imaging technique, which allows high-resolution evaluation of the anatomical features of the anterior segment of the eye regardless of optical media transparency. This technique provides diagnostically significant information in vivo for the cornea, anterior chamber, chamber angle, iris, posterior chamber, zonules, ciliary body, and lens, and is of great value in assessment of the mechanisms of glaucoma onset. The purpose of this paper is to review the use of ultrasound biomicroscopy in the diagnosis and management of rare diseases of the anterior segment such as mesodermal dysgenesis of the neural crest, iridocorneal endothelial syndrome, phakomatoses, and metabolic disorders.

Keywords: glaucoma, rare diseases, ultrasound biomicroscopy, neural crest, iridocorneal syndrome, phakomatoses, metabolic disorders

Introduction

Ultrasound biomicroscopy (UBM) is a high-resolution technique, which allows in vivo assessment of the structures of the anterior segment of the eye.1,2 Cross-sectional images of ocular structures are obtained at microscopic resolution. The commercially available transducers used in obtaining high-frequency B-scan ultrasonography images with an immersion technique operate between 35 and 50 MHz. Thus, images of the structural features of the ocular anterior segment are obtained to a depth of about 4 mm and an axial and lateral resolution of approximately 25 and 50 microns, respectively.3,4

The technique is non-invasive and efficient regardless of the clarity of the optical media and it can be performed in children with no complications.5 The internal acoustic characteristics of UBM, aided by the very fine backscatter speckle patterns at the frequencies used, permit differentiation of tissue.6 Pathologies behind anterior segment opacities can be imaged in detail with a wide gray scale that provides quantitative and qualitative information. Furthermore, UBM imaging has the capability to define relationships between the various structures of the anterior segment such as anterior chamber and angle, iris, posterior chamber, zonules, ciliary body, and lens, and is very useful in understanding the dynamics behind glaucoma.6–8 UBM visualizes anterior segment opacities in detail with high resolution and with a wide gray scale that provides quantitative and qualitative information. Moreover, UBM can be performed in children with no complications.9

Anterior segment optical coherence tomography (AS-OCT) is also used to study anterior segment structures. AS-OCT enables the acquisition of high-resolution cross-sectional images using low-coherence interferometry and infrared light, however it is...
not recommended for the study of the ciliary body because the pigmented layer of the iris does not allow transmission of infrared light. UBMs enable the visualization of the peripheral iris, ciliary body, and even the anterior choroid, and may be used to investigate the mechanisms of angle closure glaucoma in plateau iris, ciliary effusion syndrome, lens subluxation syndrome, and ciliary body cysts and tumors. The drawback of UBM is the necessity of direct contact with the eye as opposed to the non-contact, rapid technique involved in AS-OCT imaging.

This paper is focused on UBM findings in glaucoma occurring in rare diseases with a brief review of the various clinical applications.

**Methods of UBM imaging**

We have been involved in UBM imaging since 1996 at the University of Rome “Sapienza” both in the clinical management of patients and in research with an average number of 5,000 examinations. We have studied the UBM features in 48 patients with rare diseases of the anterior segment. We initially operated the Humphrey-Zeiss model 840 (San Leandro, CA, USA) (50 MHz) and presently use the Optikon HiScan Touch (Rome, Italy) (35–50 MHz) UBM system. Our method of examination is as follows: the patient is placed in a supine position and following topical anesthesia with benoxinate hydrochloride 0.4% drops, the eyelids are held open with a water-filled scleral shell and methylcellulose used as coupling agent. High-frequency scans are taken, radial and parallel to the limbus at various positions. The exam can be easily performed in an office setting and has an approximate duration of 10 minutes per eye. Cooperative children can be examined with this method in an office setting when there is a physician with broad experience with UBM. In case of infants below 2 years of age and uncooperative patients, the examination may have to be performed using general anesthesia in the operating room.

**Clinical applications of UBM**

UBM is a valid imaging method for the study of the cornea, anterior chamber, iridocorneal angle, iris, zonules, ciliary body, and the crystalline lens. Pavlin et al and Pavlin and Foster carried out the earliest studies with UBM of the anterior segment in glaucoma to investigate the etiology and mechanisms of disease in different subtypes of glaucoma. There is a large body of literature on UBM applications in glaucoma, where detailed assessment of the anterior segment, and the relationship between the peripheral iris and angle structures have been evaluated.

UBM has been used in the evaluation of cysts of the anterior segment, ciliary body, and the pars plana. Indeed, the entire anterior chamber, and the effect of the iris and/or ciliary body cysts on narrowing of the chamber angle in correspondence to the cysts can be assessed. Furthermore, UBM can measure iris and/or ciliary body cyst dimensions, anterior chamber depth, angle aperture, and trabecular-iris angle. It is also possible to differentiate between cystic and solid formations, and to assess tumor extension. In particular, cysts appear as lesions with a thin cyst wall and no solid components.

Anterior segment tumors can be studied with UBM, which gives valuable information on the extension of pigmented lesions or malignant melanoma from the iris to the ciliary body.

UBM has also been used in evaluating the cornea in dystrophies, scars, and following excimer laser photorefractive keratectomy and laser in situ keratomileusis. UBMs allow evaluation of intraocular lens implants and can detect nuclear fragments behind the iris following complicated cataract surgery. Furthermore, with the advent of intravitreal injections and steroid implants in various pathologies, it is a useful tool to evaluate complications such as injection or migration of implants in the anterior segment.

**UBM and glaucoma**

The studies of Pavlin in primary angle closure glaucoma included plateau iris syndrome and pupillary block. Examination of narrow angles in mydriasis induced by scotopic conditions can show possible appositional angle closure.

In glaucoma with pupillary block, the pressure in the posterior chamber is higher compared to the anterior chamber of the eye as opposed to the non-contact, rapid technique involved in AS-OCT imaging.
conavity. In patients with pseudophakia, UBM can help to
determine the mechanism of pupillary block glaucoma. UBM
is also an important method of imaging in glaucoma surgery
and has a central role in the follow-up of patients regarding
the filtering bleb and Schlemm’s canal.\textsuperscript{30,31}

Measurement of the anterior segment structures with
UBM is important in classifying various types of angle
closure and open angle glaucoma.\textsuperscript{32} Common biometric
parameters that are used in describing the anterior chamber
are “angle opening index”, “angle recess area”, “trabecular-
iris space area”, and “trabecular-ciliary process area”.\textsuperscript{33} These
values aid in the establishment of reproducible values for
classifying the various subtypes of glaucoma.

**Primary congenital glaucoma**

UBM allows assessment of the anterior segment morphology,
and the diagnosis of primary congenital glaucoma can be
established, especially in patients with opaque corneas, and
in infants younger than 2 years. Clinical features of primary
congenital glaucoma include: increased axial length, thin
cornea with larger diameter, deep anterior chamber, narrow
posterior chamber, reduced iris thickness, wide anterior
chamber angle, absence of iris crypts, possible anterior iris
insertion or abnormal angle membrane, and ciliary process
abnormalities.\textsuperscript{34–38} UBM usually reveals the absence of iris
crypts, which is probably caused by lack of iris sphincter
and dilator muscle, although uveal and neuroepithelial lay-
ers are preserved.\textsuperscript{39} UBM can also demonstrate elongated
and tight ciliary processes near the posterior surface of the
iris, sometimes occluding the ciliary sulcus. At times a thin
hyperreflective membrane that covers angle structures can
be visible (Barkan’s membrane).\textsuperscript{40}

Secondary glaucoma can be a complication of an array of
rare diseases classified in the following groups: conditions
with mesodermal dysgenesis of the neural crest, iridocorneal
endothelial (ICE) syndrome, phakomatoses, and metabolic
disorders. In these cases UBM can play an important role
in identifying the anterior segment alterations associated
with glaucoma.\textsuperscript{41}

**Glaucoma in mesodermal
dysgenesis of the neural crest**

The migration of neural crest cells leads to the formation of
many structural components of the ocular anterior segment,
including corneal endothelium, keratocytes, iris stroma, mel-
anocytes, and the trabecular meshwork.\textsuperscript{42} Thus, an abnormal
maturation of neuroectodermal cells can lead to various syn-
dromes involving the anterior segment. The Axenfeld–Rieger
anomaly, Peter’s anomaly, iris hypoplasia or aniridia, and
congenital glaucoma, can arise due to developmental arrest
or an altered migration of neural crest cells at a late stage
of pregnancy.\textsuperscript{42,43}

Axenfeld–Rieger syndrome is an autosomal-dominant
condition associated with mutations of \textit{PITX2, FOXC1}
shown with genetic analysis. In this syndrome glaucoma is
present in 50\% of patients. The pathogenesis is character-
ized by atypical maturation of neuroectodermal cells but an
altered primordial endothelial cell layer causing chamber
angle anomalies has also been suggested.\textsuperscript{41} Histological
sections have revealed malformations of Schlemm’s
canal and the trabecular meshwork, these alterations
coincide with the UBM features of a prominent or anterior
positioned Schwalbe’s line.\textsuperscript{42} Other characteristic UBM
features seen in this condition are iridocorneal fiber fil-
ements, high insertion of the iris into the posterior part of
the trabecular meshwork, peripheral anterior synchiae,
and atrophic iris (Figure 1).

Pathogenesis in other conditions such as Peter’s anomaly,
aniridia or iris hypoplasia, sclerocornea, and megalocornea
is linked to an abnormal anterior chamber angle leading to
impaired aqueous humor drainage.\textsuperscript{42} Sclerocornea is a rare
condition characterized by extension of sclera, conjunctival
tissue, and episcleral tissue into the clear cornea, which
leads to opacification. Typical findings are hyper-reflectivity
of the cornea, flattened cornea with thickening of the
peripheral cornea and central posterior excavation caused
by involved posterior stroma, Descemet’s membrane and
endothelium, and an abnormal Bowman’s layer which is
frequently replaced by irregular hyaline material. A number
of histological features are correlated to UBM findings in
sclerocornea (Figure 2).\textsuperscript{42}

Aniridia can be sporadic or inherited, \textit{PAX6} gene muta-
tions have been shown in non-syndromic aniridia with auto-
somal dominant inheritance and familial occurrence.\textsuperscript{44–46} The
typical UBM feature is a bilateral absence of most of the iris

\textbf{Figure 1} Ultrasound biomicroscopy image using the Humphrey-Zeiss model 840,
(San Leandro, CA, USA [50 MHz]) showing a case of Axenfeld–Rieger anomaly.
\textbf{Notes:} The anterior chamber structures present kerato-irido-lenticular contacts.
Anterior synchiae are clearly revealed (arrow heads). The ciliary body appears
adherent to the posterior iris surface (arrow).
Ultrasound biomicroscopy image using the Humphrey-Zeiss model 840 (San Leandro, CA, USA [50 MHz]) showing a case of sclerocornea with corneal thickening, irregular morphology, and internal hyper-reflectivity.


The anterior chamber is higher than that of the posterior chamber. Prior bowing of the iris because the pressure in the posterior interface to a position which is anterior to the iris root causing possible pupillary block. In UBM this is shown as an anterior bowing of the iris because the pressure in the posterior chamber is higher than that of the anterior chamber.

**Glaucoma in ICE syndrome**

ICE syndrome is a rare pathology characterized by corneal endothelial alterations, iris abnormalities, iridocorneal synechiae, pupillary displacement, and secondary glaucoma.\(^{50-52}\) ICE syndrome is classified into three clinical sub-types: progressive iris atrophy, Cogan-Reese syndrome, and Chandler’s syndrome. Various degrees of severity of iris atrophy can be detected by UBM in all forms of ICE syndrome. In mild cases, the iris is thinner than normal; in severe cases, such as in progressive iris atrophy, it can be associated with “arborised shape” of the iridocorneal angle (Figure 4).\(^{53,54}\) Corneal edema with Descemet layer folds is common, and clinical examination of anterior chamber may become difficult. UBM is an essential tool in the evaluation of angle changes in ICE syndrome where there is corneal edema.\(^{55}\) Clinical examination with both gonioscopy and UBM is useful in the characterization of peripheral anterior synechiae. Zang et al performed anterior chamber measurements with UBM which revealed peripheral anterior synechiae, and a central anterior chamber depth which was lower in patients with ICE syndrome than in normal subjects (2.25 \(\pm\) 0.32 mm versus 2.76 \(\pm\) 0.32 mm). Using UBM, these authors found that in progressive iris atrophy, peripheral anterior synechiae were less frequent, as compared to Cogan-Reese syndrome. In Chandler’s syndrome, UBM showed extensive Descemet membrane folds and corneal edema with presence of peripheral anterior synechiae.\(^{56,57}\) In any case, patients with ICE syndrome must always be periodically monitored with clinical examination including intraocular pressure measurement, gonioscopy, retina and optic nerve assessment, and visual field analysis where possible.\(^{58,59}\)

**Glaucoma in phakomatoses**

Neurofibromatosis type 1 is characterized by autosomal dominant inheritance. The major ocular alterations are Lisch nodules, optic pathway gliomas, choroidal nodules, and microvascular retinal alterations.\(^{60-63}\) Glaucoma has been reported in 1/300 afflicted patients increasing to 23% in patients with orbital-facial involvement where glaucoma is ipsilateral to the orbital-facial alterations.\(^{64}\)

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**Figure 2** Ultrasound biomicroscopy image using the Humphrey-Zeiss model 840 (San Leandro, CA, USA [50 MHz]) showing a case of sclerocornea with corneal thickening, irregular morphology, and internal hyper-reflectivity.

**Figure 3** Ultrasound biomicroscopy image using the Humphrey-Zeiss model 840 (San Leandro, CA, USA [50 MHz]) showing an eye with aniridia.

**Figure 4** Ultrasound biomicroscopy image using the Humphrey-Zeiss model 840 (San Leandro, CA, USA [50 MHz]) showing essential iris atrophy.

**Notes:** The iris is thinner than normal (arrows).
The typical anterior segment ocular features of neurofibromatosis type 1 are Lisch nodules of the iris. They are bilateral melanocytic hamartomas on the anterior surface of the iris or in the iridocorneal angle. Lisch nodules are detected in UBM as surface irregularities, characterized by oval or round medium-high reflective structures. They present a similar acoustic pattern to iris nevi. The mechanisms of glaucoma onset can be due to the presence of neurofibromas or Lisch nodules obstructing the anterior chamber, the presence of cysts, increased thickness of the ciliary body and choroid, and developmental angle abnormalities. UBM can show Lisch nodules, and abnormalities of the ciliary body and chamber angle, and help in clarifying the pathogenesis of glaucoma.

The Sturge–Weber syndrome and its variants such as the Klippel–Trenaunay syndrome are frequently associated with glaucoma. In about 60% of cases with glaucoma the cause is due to anterior chamber abnormalities, which can be assessed with UBM examination, while in approximately 40% of cases of glaucoma the cause is raised episcleral venous pressure. Clinical examination and UBM in a patient with Sturge–Weber syndrome showed supraciliary effusion of 360 degrees, and dilated superficial and intrascleral vessels with an open angle supporting the hypothesis of raised episcleral venous pressure in the pathogenesis of glaucoma. Patients with phakomatoses and especially Sturge–Weber syndrome and its variants require routine clinical follow-up for glaucoma, which can sometimes be difficult due to the young age of patients and lack of cooperation. Visual field examination can be challenging but can improve with age and learning, and the recent advent of peripapillary retinal nerve fiber layer analysis with OCT, as an early indicator of retinal nerve fiber layer loss, can be helpful in monitoring disease.

The pathogenesis of glaucoma occurring in 10% of patients with oculodermal melanocytosis may be developmental or congenital, or associated with pigmentary changes as in melanocytic glaucoma. Phakomatosis pigmentovascularis is when oculodermal melanocytosis occurs together with the Sturge–Weber or Klippel–Trenaunay syndrome and glaucoma has been reported in all afflicted patients. The mechanism of glaucoma associated with pigment dispersion was first described by Pavlin et al. and involves difficulty in trabecular outflow due to dispersion of pigment from the iris and is characterized by iris concavity in UBM.

Glucoma in metabolic disorders

Mucopepsaccharidosis, Lowe syndrome, and classical homocystinuria are rare metabolic syndromes, which can lead to secondary glaucoma. The pathogenesis of glaucoma can be congenital, or in the case of homocystinuria, can also be due to zonular abnormalities, ectopia lentis, and angle abnormalities. The use of UBM in these conditions can give detailed information on the anterior segment structures including the cornea, zonules, chamber angle, and the lens. In a case report on a rare case of mucopolysaccharidosis where corneal clouding did not allow appropriate clinical examination, UBM imaging showed corneal deposits and thickening of the corneal periphery and was fundamental in the follow-up of disease progression.

Conclusion

UBM is a valuable imaging technique for the detailed examination of the anatomical features and structures of the anterior segment of the eye, especially in the context of opacity of the anterior structures, which can greatly limit conventional clinical examination.

In the management of glaucoma, UBM is an important tool that greatly assists the ophthalmologist in the identification of the pathologic mechanisms associated with open angle, angle closure and other sub-types of glaucoma. In glaucoma associated with rare diseases of the anterior segment, such as mesodermal dysgenesis of the neural crest, ICE syndrome, phakomatoses, and metabolic disorders, UBM is especially useful as it provides valuable information on the cornea, anterior chamber, chamber angle, iris, ciliary body, zonules, and lens, allowing a complete assessment of the ocular structures.

Disclosure

The authors report no conflicts of interest in this work.

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