Possible role of standardized echography complementing ultrasound biomicroscopy in tumors of the anterior eye segment: a study in a series of 13 patients

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Abstract

Purpose To evaluate the efficacy of standardized A-scan echography (ASE) complementing ultrasound biomicroscopy (UBM) to propose the most efficient method as grounds for the diagnosis, treatment, and follow-up of anterior eye-segment tumors.

Methods The inclusion criteria were tumors of the ciliary body and peripheral choroidal tumors, whose anterior border could not be visualized with a 10 MHz ultrasound probe. The largest basal dimension and the highest prominence of the tumor were measured with a UBM Lin 50 probe. A standardized A-scan examination determined the tumor's thickness and internal reflectivity. Thus, tissue differentiation led to a standardized echography-based diagnosis (SED).

Results The study included 13 patients. SED was achieved in all examined tumors. The smallest thickness of the tumor of the ciliary body enabling SED was only 1.78 mm. The highest prominence of the tumor (3.66 ± 1.39 mm) was generally larger than its thickness (3.30 ± 1.71 mm).

Conclusion When approaching ciliary body tumors, both ASE and UBM should be performed, the former to accurately differentiate the tumor and measure its height, and the latter to delineate anterior tumor margins and iris involvement. Standardized echography-based diagnosis was grounds for further evaluation and/or treatment in this case series. The highest prominence of the ciliary body tumor perpendicular to the sclera as evidenced by UBM was generally higher than the thickness obtained with standardized echography. Hence, we propose ASE thickness to be the grounds for staging the severity of ciliary body tumors in the algorithm for their management.

Keywords Radiation plaque treatment · Standardized ultrasonography · Tissue differentiation · Uveal tumors · Ultrasound biomicroscopy

SOMMARIO

Obiettivo Valutare l'efficacia dell'ecografia standardizzata A-scan (ASE) integrandola con la biomicroscopia ad ultrasuoni (UBM) per proporre il metodo più efficiente come base per diagnosi, trattamento e verifica dei tumori del segmento oculare anteriore.

Metodi Sono stati inclusi pazienti con tumori del corpo ciliare e tumori della coroide periferici il cui bordo anteriore non poteva essere visualizzato con la sonda ad ultrasuoni 10 MHz. La dimensione basale maggiore e la sporgenza più alta del tumore sono state misurate con la sonda UBM Lin 50. L'esame ecografico standardizzato A-scan è stato utilizzato per determinare lo spessore e la riflettività interna del tumore. Pertanto, la differenziazione del tessuto ha portato alla diagnosi basata sull'ecografia standardizzata (SED).

Risultati Lo studio ha coinvolto 13 pazienti. La SED è stata effettuata in tutti i tumori esaminati. Lo spessore minimo del tumore del corpo ciliare rilevato dalla SED era di soli 1,78 millimetri. La sporgenza maggiore del tumore ($3,66 \pm 1,39$ millimetri) era generalmente più grande dello spessore del tumore ($3,30 \pm 1,71$ millimetri).

Conclusione Quando ci si avvicina allo studio dei tumori del corpo ciliare si devono tenere in considerazione entrambi i metodi ASE e UBM, il primo per differenziare accuratamente la tipologia di tumore e la sua altezza, il secondo per delineare i

marginì della parte anteriore dello stesso e per quel che riguarda il coinvolgimento dell'iride. La diagnosi basata sull'ecografia standardizzata è stata la base per un'ulteriore valutazione e/o trattamento in questa serie di casi. Come evidenziato da UBM, la più alta prominenza del tumore ciliare perpendicolare alla sclera era generalmente più elevata dello spessore rilevato con l'ecografia standardizzata. Di conseguenza proponiamo che lo spessore (rilevato col metodo) ASE funga da base per testare la severità del tumore del corpo ciliare nell'algoritmo della loro gestione.

Introduction

Ciliary body tumors often go undetected until they become large enough to produce signs and symptoms. Malignant melanoma, as the most common ciliary body malignancy, has a more aggressive course than if located elsewhere, prompting its early detection. The most efficient tool capable of providing early diagnosis and assessment of ciliary body tumors is ultrasound biomicroscopy (UBM). UBM is a crucial instrument in analyzing the localization, size, and borders of the tumor, as well as local invasion; however, it plays no role in tissue differentiation [1]. If small enough, malignant melanoma is treated conservatively with globe preservation [2]. Precise definitions of tumor margins and accurate measurements of its base and thickness are essential in the decision for optimal therapeutic procedure and radiation dosage sparing the surrounding tissue. Current guidelines stage the disease severity solely on the UBM basis [3]. On the other hand, a question is raised regarding the low interobserver reproducibility of UBM measurements [4, 5], consequently emphasizing the need for the revision of current guidelines. A-scan standardized echography (ASE) yields more precise measurements of tumor thickness and is the only method allowing tissue differentiation analysis [6–8].

Given the above specified concerns and complementing effects of UBM and ASE, thorough literature search was performed, revealing a single study on standardized echography complementing UBM [1]. In the aforementioned study, tissue differentiation only included five pigmented ciliary body tumors that were ≥ 4 mm thick.

Hence, a prospective study was set up to evaluate the efficacy of standardized A-scan echography complementing UBM to propose the most efficient method as grounds for the diagnosis, treatment, and follow-up of anterior eye-segment tumors.

Materials and methods

A prospective study was conducted at University Eye Clinic, Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, University Hospital "Sveti Duh", Zagreb, Croatia, from November 2013 to May 2016.

The inclusion criterion for the study was a newfound tumor of the ciliary body and the peripheral choroid with anterior borders that were unreachable with a 10 MHz ultrasound probe. The exclusion criteria were ciliary body tumors already treated and those confined only to the iris.

Patients were examined with a UBM Lin 50 probe (Aviso, Quantel Medical, Paris, France), followed by a standardized A-scan examination (Aviso S, Quantel Medical, Paris, France).

A UBM probe, closed with ClearScan filled with sterile distilled water, was used while the patient was sitting. A contact ASE was performed in supine position. Both examinations were done using topical tetracaine drops (tetracaine ophthalmic drops), always by the same examiner.

The largest basal dimension and highest prominence of the tumor (TP) perpendicular to the sclera, including scleral thickness, were measured with UBM. The tumor thickness (TT) and internal reflectivity were determined with a standardized A-scan examination. The involvement in clock hours was documented.

The tumor Q-1 function of the ASE machine evaluates the reflectivity by measuring the surface covered by the echoes between two markers set on the tumor margins. Two values are displayed: *Quant-I (T)*, the surface limited mainly by peaks of the echoes at tissue *Gain (T)*; and *AVG Height*, the surface limited by echoes (peaks and valleys). The *AVG Height*, combined with specific ultrasound characteristics corresponding to each uveal tumor, described by Ossoinig [6–8], results in tissue differentiation. This derives standardized echography-based diagnosis (SED), which directs further diagnostic procedures and treatment. UBM and standardized echography were routinely performed in the follow-up.

The study was conducted with the approval of the local research ethics committee and complies with the tenets of the Declaration of Helsinki.

Informed written consent was obtained from all patients prior to their inclusion in the study. Descriptive statistics were used for data evaluation.

Results

Descriptive statistics are shown in Table 1. Thirteen patients met the study criterion; nine were women.

Table 1 Descriptive statistics

No	Sex	Age (years)	Right/left eye	Clock hours	BD (mm)	TP (mm)	TT (mm)	AVG height (%)	SED
1	F	78	R	6:30–8:0	7.57	3.09	1.94	63	MMCB
2	M	58	R	4:0–6:0	9.09	6.75	6.08	22	MMCB
3	F	60	R	4:0–5:0	3.53	3.59	2.63	59	MMCB
4	M	61	R	3:0–4:0	5.13	4.16	3.33	54	MMCB
5	F	68	L	8:0–9:30	8.0	2.49	2.25	62	MMCH
6	F	38	R	6:30–7:30	1.95	2.72	2.63	56	MMCB
7	M	70	R	8:0–9:0	4.05	3.11	2.67	78	MetaCB
8	F	42	R	4:0–5:30	7.74	1.79	1.39	48	MMCH
9	M	71	R	6:0–7:30	6.72	5.54	7.40	54	MMCB
10	F	61	L	6:0–7:0	6.12	3.44	3.29	78	Leiomyoma CB
11	F	62	L	5:0–5:30	2.93	3.34	4.11	79	MetaCB
12	F	78	L	5:30–6:0	3.11	5.15	3.45	60	MMCB
13	F	71	R	7:0–9:0	5.11	2.47	1.78	66	MMCB

F female, *M* male, *Clock hours* location of the tumor, *BD* the largest basal dimension of the tumor measured by UBM in millimeters (mm), *TP* the highest prominence of the ciliary body tumor perpendicular on sclera, including scleral thickness, measured by UBM in mm, *TT* the tumor thickness measured on standardized echography in mm, *AVG Height* the reflectivity calculated by measuring the surface covered by the echoes between two markers set on the tumor margins (peaks and valleys) in percentage, *SED* standardized echography-based diagnosis, *MMCB* malignant melanoma of the ciliary body, *MMCH* malignant melanoma of the choroid, *metaCB* metastasis of the ciliary body, *leiomyoma CB* leiomyoma of the ciliary body

There were 11 tumors of the ciliary body and 2 of the peripheral choroid. Among the ciliary body tumors, there were eight SED malignant melanomas, two metastatic tumors, and one leiomyoma. Both peripheral choroid tumors were SED malignant melanomas.

The average basal dimension of the ciliary body tumors was 5.46 ± 2.26 mm (median 5.13 mm) and the TP 3.66 ± 1.39 mm (median 3.34 mm), while the average TT was 3.30 ± 1.71 mm (median 2.67 mm). The smallest

tumor thickness of the ciliary body tumors that allowed tissue differentiation on ASE was only 1.78 mm (Fig. 1).

The internal reflectivity of the SED malignant melanoma of the ciliary body and the choroid was 22–66%; of SED metastasis, 78 and 79%, respectively; and of leiomyoma, 78%. Patient number 10 (Table 1) had a nonpigmented ciliary body tumor diagnosed in 2011 in another clinic. Upon the initial UBM at our clinic in 2014, a clearly delineated, homogenous, high-reflective mass was found within a surrounding residual low-reflective ciliary body tissue.

Fig. 1 **a** UBM of 71-year-old female with ciliary body tumor. **b** The smallest SED malignant melanoma of the ciliary body of 1.78 mm

It appeared as a rounded mass in the supraciliary space, between the uvea and sclera, as if it did not arise from the uveal stroma (Fig. 2a). On standardized echography, the tumor had a high reflectivity of 78% and a homogenous internal structure (Fig. 2b) with signs of vascularisation. It showed no progression in size. Numerous high-reflective lesions such as leiomyoma [9, 10], melanocytoma [9], medulloepithelioma [11], adenoma [12–14], pseudoepitheliomatous hyperplasia, haemangioma, and neurofibroma [9] were considered a differential diagnosis. Based on clinical findings and ultrasound characteristics, SED leiomyoma was established. It was closely followed as neither progression nor symptoms were expected to develop.

Fine-needle aspiration cytology was performed only in two patients of the study group, both with SED metastatic ciliary body tumors. Patient number 7 (Table 1) had a large ciliary body tumor presenting as a lobulated mass on UBM, while the irregular internal structure of high reflectivity on standardized echography revealed metastasis. The UBM finding was almost identical to one of our earlier cases, histopathologically proven to be small-cell lung carcinoma (SCLC) metastasis (Fig. 3). Namely the lobulated internal structure of the tumor might reflect histopathological characteristics of SCLC: the nested or organoid pattern and peripheral palisading of tumor cell nests [15]. Fine-needle aspiration confirmed the diagnosis. In the second patient,

Fig. 2 **a** UBM of 61-year-old female shows clearly delineated, homogenous, high-reflective mass within the surrounding residual low-reflective tissue of the ciliary body. It appeared as a rounded mass in the supraciliary space between the uvea and sclera, as if it

did not arise from the uveal stroma. **b** Standardized echography of the tumor reveals high reflectivity of 78% and homogenous internal structure. SED was leiomyoma

Fig. 3 **a** A ciliary body tumor with a lobulated internal structure was found on the UBM of a 70-year-old male. **b** High reflectivity and irregular internal structure on standardized echography indicated SED metastasis

cytology was inconclusive, prompting further search for primary malignancy.

All but one patient with SED malignant melanoma of the ciliary body were immediately referred for plaque radiation therapy. One patient underwent enucleation because of secondary absolute neovascular glaucoma.

Discussion

The role of UBM in the diagnosis of anterior eye-segment tumors is well established [16–18]. However, its major limitation addresses accuracy in providing a definite diagnosis of the disease as it is not a standardized ultrasound technique and has no potential for tissue differentiation [1, 6]. ASE is the only clinically available noninvasive method allowing tissue differentiation in agreement with histopathological identification [6–8]. Hence, only when these two methods are combined full diagnostic value could be reached: locating the tumor; documenting its clock-hour involvement, dimensions, borders, and local invasion; and differentiating the tissue. Clinical application is evident in the SED of uveal melanoma, which does not need to be biopsied but immediately undergoes treatment [3].

In our study, UBM was used to document the localization and size of the lesion, providing no information on tissue differentiation. However, ASE quantitatively measured internal reflectivity and set the grounds for final diagnosis in all patients. Low internal reflectivity and vascularisation distinctly defined malignant melanoma; hence, no histopathological verification was required. Patients with presumed malignant melanoma were straightforwardly treated with brachytherapy. On the other hand, high internal reflectivity

and no signs of vascularisation combined with characteristic patterns prompted us to rule out metastases by performing fine-needle aspiration biopsy in two patients. One patient with a nonprogressive lesion and findings, indicative of leiomyoma on standardized echography, was thus only followed.

Tissue differentiation with standardized echography can be obtained for choroidal tumors only 1.0 mm thick [6]. However, no reliable data exist for the ciliary body tumors. The only published study documented tissue differentiation of tumors ≥ 4.0 mm [1]. In our study, the smallest ciliary body tumor being differentiated on standardized echography was only 1.78 mm thick.

These case series results raise concern for the value of UBM as the sole method for staging the severity of the disease [3] as evidenced by the discrepancy in measurements between UBM and standardized echography.

The highest prominence of the ciliary body tumor perpendicular to the sclera measured by UBM was higher than the thickness of the same tumor obtained with standardized echography in all but two patients. There are more reasons for that. First, TP obtained with UBM is the highest prominence of the tumor perpendicular to the sclera and includes both the conjunctiva and the sclera. It means that 238.8 ± 51.1 μm for bulbar conjunctiva [19] and 0.50 ± 0.11 mm of thickness of the sclera at limbus [20] should be subtracted from the UBM measurement to approximate the thickness of the tumor. Furthermore, perpendicularity is affected by the observer's subjective interpretation. Last but not least, the posterior border, especially in large tumors, is poorly defined because of sound attenuation (Fig. 4). The latter is the main reason for higher TT than TP in the two patients.

On the other hand, ASE biometry is precise because of the well-defined perpendicularity of echo spikes delineating

Fig. 4 **a** UBM of 71-year-old male with ciliary body tumor. Note poorly defined posterior border of the tumor. **b** Consequently, the tumor thickness on the standardized A-scan examination is higher

than the highest prominence of the tumor perpendicular to the sclera measured on UBM. SED was malignant melanoma

the tumor borders [7]. This discrepancy in measurements draws attention to the fact that therapeutic radiation plaque dose calculation is based on the tumor UBM dimensions and depth [21]. According to the current guidelines, for patients with small T1 uveal melanomas, follow-up for growth is recommended [3]. For patient numbers 1 and 13 (Table 1), the discrepancy between UBM and ASE tumor dimensions could have misguided the therapeutic intervention and improperly pinned a survival prognostic indicator if only the UBM analysis would have been taken into account. Clearly, we lack the precision in describing uveal melanomas. A similar problem was encountered by Nicholson et al. [22], who studied the relationship between histologic tumor thickness and ASE thickness and set the echographic rather than histologic measurements as a referent standard for defining outcome predictabilities because of inconsistent tissue shrinkage induced by fixation procedures during histologic preparation. Keeping all this in mind, we believe that an amendment of the current guidelines [3, 21] of ciliary body tumors could be considered if this study's results will be confirmed in a large series.

Choroidal tumors whose anterior border could not be visualized with a 10 MHz ultrasound probe must be examined with UBM to establish its relation to the ciliary body. In our study, both tumors were adjacent to the ciliary body, 1.26 and 0.66 mm, respectively.

Women show greater involvement of the ciliary body and iris with uveal melanoma than men [23]. In this study population, anterior eye-segment tumors were generally more common in females. However, ciliary body melanomas were equally represented in both sexes (Table 1). Apart from the 38-year-old female, the patients with ciliary body melanoma in our study were 58–78 years old, according to the literature [18].

A primary malignant melanoma may be located in any quadrant of the ciliary body, unlike those of the iris, generally present only in the lower half of the eye [9]. All tumors in this study population were located in the lower half of the eye, mainly from three to nine o'clock, and affected not more than two and a half hours. Only one tumor, an SED malignant melanoma of the choroid, spread to nine-thirty.

In choroidal tumors, standardized A-scan measurements provided very reproducible results [24]. On the contrary, the interobserver reproducibility of the UBM varies considerably, notably for the less defined structures [4, 5]. Therefore, all the measurements performed in this study were undertaken by only one examiner.

The strength of this study is the relatively large series of very rare tumors, compared to the only published report dealing with this issue, which analyzed five patients [1]. However, sample size could also be seen as a study limitation, considering the variety of differential diagnoses in ciliary body tumor investigations. Another strength of the

study is that all tumors were measured and diagnosed by one skilled investigator experienced in UBM and standardized echography, leaving no room for interobserver reproducibility issues.

Given the study's limitations, tumor characterization is based solely on imaging features in the majority of patients. Although this is the standard management for patients with tumors of the ciliary body, this limits the strength of the work because biopsy is the only diagnostic method that confirms the tumor histopathology. However, in a clinical setting, a biopsy is indicated when less invasive methods cannot establish the diagnosis for presumed metastasis and on the patient's request [9]. On the other hand, standardized echography is a well-established noninvasive technique that gives reliable results in tissue differentiation. In all our patients with SED malignant melanoma, we found no justification for biopsy since, according to the guidelines, clinical diagnosis is adequate for treatment with no need for histopathologic verification [3]. A UBM complemented with low- and high-frequency ultrasound imaging increased the accuracy of the clinical diagnosis. In our opinion, the absence of a biopsy did not impact the study results and conclusion.

Conclusion

When approaching ciliary body tumors, both ASE and UBM should be performed, the former to accurately differentiate the tumor and measure its height, and the latter to delineate anterior tumor margins and iris involvement. The smallest ciliary body tumor that could be differentiated with a standardized A-scan was only 1.78 mm. A standardized echography-based diagnosis was grounds for further evaluation and/or treatment in this case series. The highest prominence of the ciliary body tumor perpendicular to the sclera as evidenced by UBM was generally higher than the thickness obtained with standardized echography. Taking into account the poor interobserver reproducibility of UBM measurements compared to ASE, the ASE tumor thickness should also be included as grounds for staging the severity of ciliary body tumors in the radiation plaque treatment algorithm.

Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

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