Discussion

Discovery of a pattern of formation of mushroom-shaped tumors: a new approach to the study of intraocular melanomas

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Відкриття закономірності формування грибоподібних пухлин: новий підхід до вивчення внутрішньоочних меланом

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Abstract

The main purpose and motivation for this study was the assumption that intraocular mushroom-like melanomas, the spherical part of which is located outside the choroid, may have a retinal nature.

This work is a retrospective study based on a preliminary investigation of histomorphological material with subsequent qualitative analysis. The work proposes a theoretical approach to solving a scientific problem, when the answer to the question of the histogenesis (place of origin) of the tumor is given not by studying histological patterns, but by analyzing the theoretical model of mushroom-like tumor formation.

The theoretical model allows us to understand that no uveal tumor can form a mushroom-like nodule. Based on this, we formulated a pattern of formation of intraocular mushroom-like tumors, according to which the initial growth of a mushroom-like intraocular neoplasm is always associated with the spherical part, and the uveal part is a secondary place of their growth. This pattern applies to mushroom-like tumors of any localization. The specificity of intraocular mushroom-shaped tumors is that the growth of their spherical part is impossible without penetration into the choroid. This feature distinguishes them from mushroom-shaped tumors of other localizations, and this is one of the main reasons why their histogenesis has been difficult to detect.

It has been shown that the mushroom-shaped tumor cannot originate from the choroid. This would be contrary to the laws of physics, not to mention the biological constraints regarding the growth pattern of tumors. The theoretical model of the mushroom-shaped melanoma suggests that its origin is linked to the retinal pigment epithelium. So, we are faced with the need for a fundamental revision of the classification and nomenclature of intraocular melanomas, which should be the next step.

Keywords: *intraocular melanoma, mushroom tumors, retinal pigment epithelium, discovery.*

Резюме

Головною метою та мотивацією для цього дослідження було припущення, що внутрішньоочні грибоподібні меланоми, сферична частина яких розташована поза судинною оболонкою, можуть мати ретинальний характер.

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Ця робота є ретроспективним дослідженням, заснованим на попередньому вивченні гістоморфологічного матеріалу з подальшим якісним аналізом. В роботі пропонується теоретичний підхід до вирішення наукової проблеми, коли відповідь на питання про гістогенез (місце походження) пухлини дається не шляхом вивчення гістологічних закономірностей, а шляхом аналізу теоретичної моделі формування грибоподібної пухлини.

Теоретична модель дозволяє зрозуміти, що жодна увеальна пухлина не може утворити грибоподібний вузол. На основі цього ми сформулювали закономірність формування внутрішньоочних грибоподібних пухлин, згідно з якою початковий ріст грибоподібного внутрішньоочного новоутворення завжди пов'язаний зі кулястою частиною, а увеальна частина є вторинним місцем їх росту. Ця закономірність стосується грибоподібних пухлин будь-якої локалізації. Специфіка внутрішньоочних грибоподібних пухлин полягає в тому, що ріст їх кулястої частини неможливий без проникнення в судинну оболонку. Ця особливість відрізняє їх від грибоподібних пухлин інших локалізацій, і це одна з основних причин, чому їх гістогенез було важко виявити.

Було показано, що грибоподібна пухлина не може походити з судинної оболонки. Це суперечило б законам фізики, не кажучи вже про біологічні обмеження щодо характеру росту пухлин. Теоретична модель грибоподібної меланоми припускає, що її походження пов'язане з пігментним епітелієм сітківки. Отже, ми стикаємося з необхідністю фундаментального перегляду класифікації та номенклатури внутрішньоочних меланом, що має стати наступним кроком.

Ключові слова: *внутрішньоочна меланома, грибоподібні пухлини, пігментний епітелій сітківки, відкриття.*

Introduction

Over the century and a half that have passed since the beginning of histomorphologic study of intraocular tumors, which began in the mid-19th century, the opinion about choroidal melanoma as the only representative of intraocular pigmented neoplasms has become firmly rooted. This confidence is due to the actually observed histotopographic connection of intraocular melanomas with the choroid, where melanocytes, a potential histogenetic source of such neoplasms, are located. However, in addition to melanocytes, pigment epithelium is another potential source of melanomas in the eye. The pigment epithelium is closely associated with the choroid, so that until the beginning of the last century it was often called the pigment epithelium of the choroid. Indeed, the embryogenesis of the pigment epithelium is related to the retina, but, anatomically, it is associated with the choroid and is separated from its stroma and capillary vascular network by the collagen-elastic Bruch's membrane with a thickness of no more than 2-4 μm, which is barely visible under light microscopy. Thus, the distance between the cells of the pigment epithelium and the melanocytes of the inner layers of the choroid in some areas is smaller than the size of the cells themselves. This raises a logical question about how accurately one can establish the type of pigment cells - the source of intraocular melanomas, if the melanocytes of the choroid and the cells of the pigment epithelium of the retina are not only located, figuratively speaking, back to back, but are also tightly connected anatomically. It is important to consider that the pigment epithelium is represented by a cellular monolayer without its own stroma and vessels; therefore, its trophic needs are satisfied by the choroid. The latter circumstance predetermines that pigment epithelial neoplasms cannot grow without stromal-vascular support from the choroid. However, this most important factor determining the growth characteristics in unusual intraocular conditions has never been taken into account before. This is despite the fact that tumors from the pigment epithelium and uveal melanocytes doomed to grow in the same anatomical space and both cell types are capable of pigmentation. A similar situation during differentiation of melanogenic tumors does not arise outside the eye. In most cases, the presence of pigmentation and, if necessary, appropriate immunohistochemical markers, as a rule, are sufficient to establish the diagnosis of melanoma. However, knowing that melanomas can develop in the eye from two different cellular sources, the researchers did not consider it important to discuss the criteria for differentiating the two types of melanogenic tumors in the eye. In this regard, it should be noted that back in 1894, J. Griffiths, examining an enucleated eye with advanced intraocular melanoma, which soon led to the death of the patient, verified it as a tumor of the retinal pigment epithelium [1]. It is obvious that the author proceeded from a character of the histological patterns of this tumor. Sometimes, such patterns had similarities with those of metaplastic transformations of the pigment epithelium in post-traumatic growths inside the eye. Griffiths'article remained out of discussion for a long time, until Andersen and Reese in the middle of the last century drew attention to this article and stated that the case described by Griffiths was in fact a uveal melanoma [2-3]. Based on his own clinical and morphological observations, Reese claimed that the retinal pigment epithelium is generally not capable of malignant transformation, and only occasionally can produce tumor-like proliferates of a benign nature [4]. The authority of Reese, as a leading specialist in the field of ophthalmic oncology and eye pathology, contributed to the formation of a stereotype in understanding the histogenesis of intraocular melanomas, which practically excluded the prospect of finding a histogenetic connection between the retinal pigment epithelium and intraocular melanomas. So, now, after many decades, when neither clinicians nor pathologists feel uncomfortable regarding intraocular melanomas as choroidal tumors, it is difficult to imagine what might prompt a change in the entrenched view of their origin.

Design features of this theoretical study

This study began with the assumption that intraocular mushroom-shaped tumors, the spherical part of which is located outside the choroid, could have a retinal origin. Initially, it was only a desire to find fundamental histomorphological differences between mushroom-shaped melanomas and those that grow exclusively in the choroid. Although this working hypothesis was later proven untenable, it stimulated and supported a long-term histomorphological study, during which more than a thousand samples of intraocular tumors were studied. The solution arose unexpectedly and was not associated with the histomorphological samples studied. It can be characterized as an intuitive image or virtual model, which concentrated the essence of the quest. This solution can be expressed by the thesis: "a choroidal tumor cannot form a mushroom-shaped node."

The design of this work can be characterized as a retrospective investigation based on the previous study of archival histomorphological material followed by qualitative analysis. It is important to note that the emerged idea cannot be substantiated by histomorphologic examination. However, it is also hard to imagine how, without being involved in the histomorphological study of melanomas, one could come to such a conclusion. At the same time, the decision itself and its verification are not the prerogative of histomorphologists, but are within the competence of everyone who has a basic medical education, and especially with knowledge of the clinical anatomy of the eye and general oncology. Furthermore, the formation of a spherical nodule, under conditions similar to those attributed to intraocular melanoma, is determined by physical laws, suggesting the impossibility of spatial displacements that could lead to the formation of a mushroom-shaped tumor from the choroid. This will allow representatives of the exact mathematical sciences to be equally experts in assessing the main idea about the possibility of the formation of a mushroom-shaped form when a tumor spreads from the choroid. It is interesting to note that not so long ago, a well-known European ophthalmological journal published an editorial with the wish that ophthalmology would one day find a place for theoretical solutions similar to those that revolutionized physics in the last century [4]. This article offers an example of a theoretical approach to solving a scientific problem.

Therefore, we need to prove that a choroidal tumor cannot form a mushroom-shaped node. As it is well known, the negative judgment, which became the main element of the discovery, cannot be the subject of proof. According to the laws of logic, in such cases, proof is reduced to refuting the antithesis, what is called contradiction in contrarium. So, we are talking about a judgment that is still considered true: "a choroidal tumor in the process of its development forms a mushroom-shaped node." In classical logic, such a proof is based on the truth of the law of double negation.

Critique of the existing model of intraocular mushroom melanoma formation

The seemingly most obvious conclusion is that epichoroidal node originates from the choroidal node, which is common for all forms of intraocular melanoma. On this basis, a purely mechanistic explanation for the formation of the intraocular mushroom node was constructed, without taking into account the biological properties of neoplasm and the real physical forces that determine the tumor shape. Therefore, the position of physics and mechanics prevails when considering the existing concept, especially since mechanistic approach dominates the generally accepted explanation of intraocular mushroom melanoma.

As evidenced by numerous authoritative sources, which are quoted from the middle of the last century up to the present day, the mushroom-shaped node is formed as a result of stretching and subsequent rupture of Bruch's membrane, after which the tumor spreads unhindered in the subretinal space, taking on a spherical shape [5]. It should be emphasized that the accepted explanation ignores the invasive capabilities inherent in malignant tumor, such as intraocular melanoma, due to which tumor can penetrate through denser anatomical barriers than Bruch's membrane. Thus, the accepted explanation of the intraocular mushroom shape is based on the justification of only one defect at the apex of the uveal node due to the supposed stretching of Bruch's membrane. Of course, it cannot be denied that with the growth of the uveal node the length of Bruch's membrane can become longer than the original. However, the conditions under which this occurs have never been discussed. The previously accepted explanation assumed that any prominence of the choroidal tumor on the eye fundus leads to an increase in the length of Bruch's membrane and, consequently, to its stretching. However, this would be true only if Bruch's membrane were located on a horizontal plane, as shown by the dotted line in the Figure 1. In reality, Bruch's membrane is located on the concave surface of the eyeball, determined by the curvature of the sclera and the choroid lying on it. During the growth of the uveal node, Bruch’s membrane moves from a concave to a convex position over a certain period of time, and its length can remain the same even with a relatively large protrusion of the tumor node (Fig. 1). Thus, from the very beginning of the analysis of the existing view on the origin of intraocular mushroom melanomas, we are faced with a serious contradiction: Bruch's membrane does not stretch with the growth of the uveal node until it reaches a size that is significantly larger than that characteristic of most mushroom melanomas.

Thus, as can be seen from the schematic interpretation presented in the Fig. 1, the rupture of Bruch's membrane due to an increase in its length cannot be considered a necessary condition for the formation of a mushroom-shaped node. Although individual variants of mushroom-shaped melanomas do not exclude the possibility that stretching of Bruch's membrane could have taken place, there are

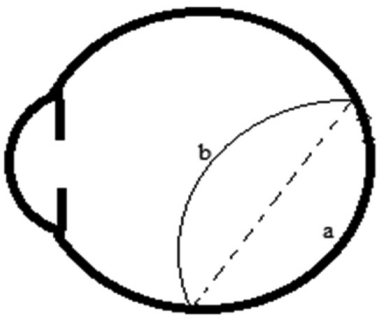

Figure 1. Schematic interpretation: initial position of Bruch's membrane near the sclera – (a) and on the surface of the tumor node – (b). When comparing these two arches, it is evident that the length of Bruch's membrane has not increased in top position, despite the significant size of the tumor node.

many opposite examples when this mechanism is absolutely unrealistic. Thus, Figure 2 shows two examples: a mushroom-shaped melanoma formed with an extremely flattened uveal node, which excludes a rupture of the Bruch's membrane, and a metastasis to the choroid with an extremely high protrusion of the tumor, but without the formation of a mushroom-shaped node. The latter tumor was described by us earlier as a rare variant of metastasis of neuroendocrine lung carcinoma, confirmed by immunohistochemistry [6]. This case is also interesting due to the extremely high protrusion of the tumor node, which is not typical for uveal metastases. On the surface of the tumor node, defects of the Bruch's membrane were revealed in the form of its disorganization and replacement by tumor cells against the background of desquamation of the pigment epithelium and pronounced cystic degeneration of the retina. Similar defects have been described not only above metastatic nodes, but also in melanomas, and without any connection with the formation of a mushroom-shaped node [7]. It should be noted that it has never been discussed before how such defects differ from alleged ruptures and why they do not lead to the formation of a mushroom-shaped tumor. After all, in this case, it would be necessary to admit the possibility of the formation of several epichoroidal spherical nodes, which is never observed. Also, the formation of mushroom-shaped uveal metastases due to the rupture of Bruch's membrane is never observed, which is already a reason to think about the origin of mushroom-shaped melanomas. However, all the above facts were strangely ignored, and only those that did not contradict the idea of the uveal origin of melanoma were taken into consideration. In addition, all the arguments that were used to explain the formation of mushroom-shaped melanoma turn out to be untenable. Of course, the fallacy of the explanations does not exclude the possibility that intraocular mushroom-shaped melanomas are formed from the choroid, but in another, as yet unknown way.

At the same time, in retrospect, assessing the current situation, it should be noted that in this case, what is taking place is not just a common misconception but a kind of collective cognitive dissonance, when justification is sought for a concept that has become habitual over a century and a half. It was precisely because of this cognitive dissonance, it was completely "forgotten" that mushroom-shaped tumors are present not only inside the eye. And if we turn to mushroom-shaped tumors of other localizations, we will see the opposite picture: everywhere the spherical part is the site of the initial tumor growth.

As it is known, mushroom-shaped tumors of the skin, respiratory and gastrointestinal tract, mucous membrane of the urinary bladder, endometrium and others originate exclusively from the cellular elements of the integumentary epithelium and adjacent stroma, i.e. everywhere the beginning of tumor growth is located in the upper spheri-

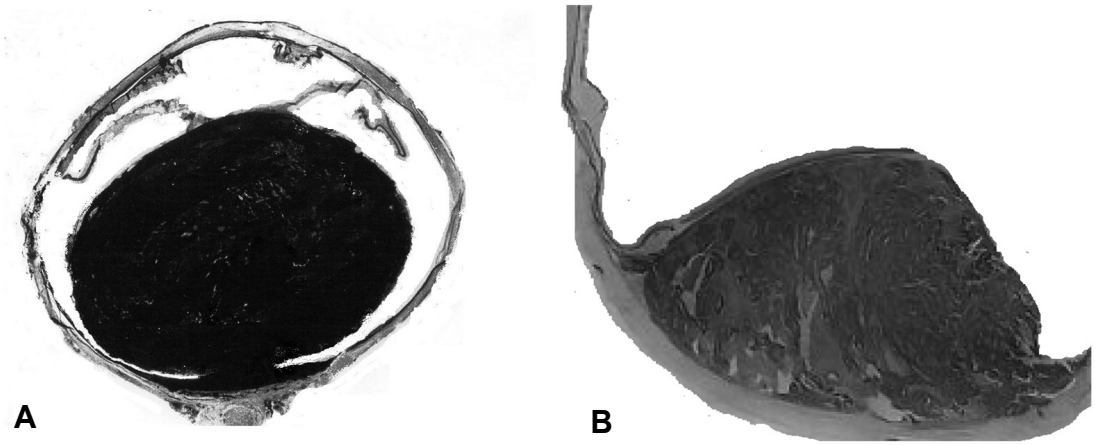

Figure 2. A. General view of a mushroom melanoma on a histological section. With such protrusion of the uveal node, stretching of Bruch's membrane is impossible. **B**: unusual variant of uveal metastasis, high prominence of the tumor node (1) with undoubted stretching of Bruch's membrane but without a tendency to mushroom growth, (2) – retina with cystic degeneration covers the top of the tumor node. Photographs from stained celloidin (top) and paraffin histological sections.

cal part, and not in the underlying deep tissues. Nothing is known about any breakthrough of fascial or membrane structures in connection with the formation of the mushroom-shaped tumors beyond the eyeball. Of course, destruction and defects of the border structures also occur here. However, such defects lead to ulceration if there are no other tissues above the defect in which tumor growth could continue. According to the existing explanation of the formation of intraocular mushroom melanomas, after the supposed breakthrough of Bruch's membrane, the tumor spreads unhindered in the subretinal space. This is another misunderstanding that supports the current notion of intraocular mushroom melanoma. In furtherance of this absurd thesis, many authors, including such an authority as A. Reese, have specifically cited examples showing detached retina that allegedly is not associated with the tumor node. At the same time, examples of the growth of the spherical part exclusively in the retina are known and also were not refuted anywhere. These variants are in no way associated with the general mechanism of the formation of intraocular mushroom melanoma (Fig.3). However, the existing explanations for the formation mechanism of intraocular mushroom melanomas bypass how such intraretinal nodules form, given the inevitable detachment and cystic degeneration of the retina before the “breakthrough” of Bruch’s membrane. Moreover, this applies equally to both nodular-flat melanomas and metastases, which never take a mushroom-shaped form, despite equal opportunities to cause destructive changes in Bruch's membrane.

Of course, the idea of uveal origin of melanoma was finally formed at the beginning of the last century, when the features of invasive tumor growth were still poorly known. In particular, there was no data on tumor growth in vitro, which clearly showed that tumor cells (as well as most others) were not capable of dividing in a liquid medium, without attachment to a solid substrate.

Perhaps in connection with this, the absurd assertion that after rupture of Bruch's membrane, intraocular melanoma spreads in the subretinal exudate under the retina was accepted and subsequently remained unnoticed. Everywhere and always, tumor growth represents an invasion, i.e. penetration into the tissue structure that has a stroma and vascular network, without which further tumor growth is impossible. The case shown in Fig. 3 fully meets this requirement. However, the question remains: where is the initial point of growth - in the spherical (retinal) part (as in all known mushroom-shaped tumors) or in the uvea, as suggested by existing ideas about intraocular melanomas? Here we will ignore, for now, the fact that the existing concept practically does not consider the participation of the retina in the formation of the spherical node. Let us assume that the tumor spreads in the tissue environment after the rupture of Bruch’s membrane, which corresponds to modern concepts of tumor growth. Can such growth lead to the formation of a spherical node if the tumor originates from the choroid?

A realistic model for the formation of intraocular mushroom-shaped tumors

When modeling, it is necessary to proceed from the fact that tumor growth inward from Bruch's membrane occurs in a homogeneous environment. The spread of the tumor continues in the thickness of the choroidal tumor node, which can also be considered a homogeneous environment, although with a different density. As it is known, in a homogeneous environment, a tumor always tends to take on a spherical shape, since it is the sphere that is the geometric locus of points equally distant from the center. The diagram in Fig. 4 shows that the tumor continues to spread evenly in all directions at the point of rupture of Bruch’s membrane, so that the front of tumor growth on both sides of Bruch's membrane can be represented by hemispheres

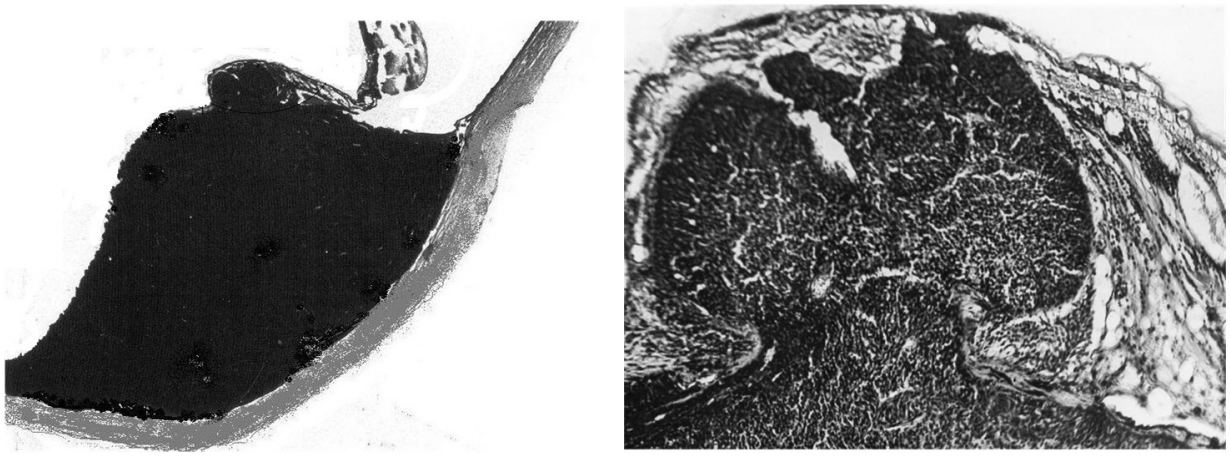

Figure 3. A rare variant of intraocular mushroom melanoma that refutes the thesis that after rupture of Bruch's membrane, uveal melanoma spreads under the retina. Top: general view of a mushroom-shaped melanoma (stained celloidin histological section). Below: the histological picture of this retinal nodule shows that the spherical part is completely localized in the retina. Magnification 40X.

1 and 2. There is no need to discuss here that the rate of tumor growth in the choroid and above Bruch's membrane may be different; however, the site of the Bruch's membrane rupture is the center of the tumor mass that forms on both sides of Bruch's membrane. In reality, which many intraocular mushroom-shaped tumors represent, their front of spreading above Bruch's membrane corresponds to sphere 3. In order for a tumor spreading from a rupture point of Bruch's membrane to take this form, a special external influence or physical forces are required. A physical interpretation of such a process can be the inflation of a balloon. Thus, if we assume that there is a stretching shell above the rupture site, then it becomes quite clear why the front of spreading of the physical mass has a spherical shape (position 3 in Fig. 4). This explanation highlights the complete absurdity of both the existing concepts of the formation of intraocular mushroom-shaped melanoma and the very assumption that mushroom-shaped growth from the choroid is possible.

Thus, there is absolute proof that mushroom intraocular melanoma cannot originate in the choroid. It becomes obvious that the histogenetic source of these melanomas can only be the pigment epithelium. As already noted, mushroom melanomas and melanomas without epichoroidal growth have a similar histological structure, so there has never been any doubt about their common origin. However, at present we have no reason to change our opinion to the opposite with respect to all cases of intraocular melanoma, especially since benign melanomas of unconditional uveal genesis are known. A new round of comparative histological and histochemical studies will be required to ensure that among melanomas that do not spread beyond Bruch's membrane, there are variants that are histogenetically unrelated to mushroom melanomas. After all, melanomas arising from the pigment epithelium can have either a mushroom-shaped or flattened - nodular form, whereas uveal tumors can only have a flattened - nodular form. Uveal metastases always have the same form, never forming a tumor nodule beyond Bruch's membrane, although, as shown above, they are sometimes capable of reaching a much greater prominence than most melanomas. By the way, the example of uveal metastases is a confirmation that mushroom-shaped growth from the choroid is impossible. Of course, the absence of mushroom-shaped choroidal metastases cannot be proof of the fundamental impossibility of such phenomenon. Nevertheless, this circumstance makes the concept of the formation of intraocular mushroom-shaped melanoma presented here a scientific theory, what cannot be said about the existing idea of the uveal origin of melanoma. As it is known from the point of view of the philosophy of science, one of the most important criteria for classifying any concept as scientific knowledge is its falsifiability (the so-called K. Popper criterion), i.e. the potential opportunity of refutation through experiment or observation. So, the refutation of our concept could be the detection of the formation of a mushroom-shaped tumor as a result of the rupture of Bruch's membrane by a uveal metastasis. After all, given the complete failure of explanations for the mechanism of formation of mushroom-shaped intraocular melanoma, the absence of mushroom-shaped uveal metastases does not become a reason to abandon the old view against the background of endless expectation that at some point the metastasis may turn out to be mushroom-shaped. Like this a pseudo-theory can ignore any fact and not notice any refutation, based solely on habit, an established stereotype and partly on banal stubbornness.

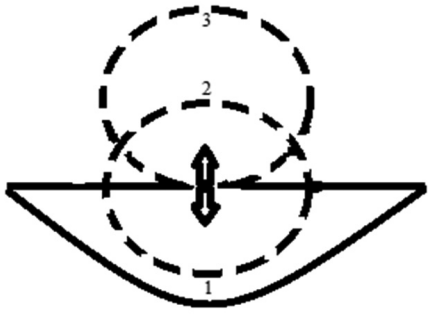

Figure 4. Schematic illustration of possible tumor spread after Bruch's membrane rupture. Arrows indicate two directions of growth at the site of Bruch's membrane rupture – dotted line 1 shows the growth front in the choroid, 2 – epichoroidal growth. 3 – tumor growth front corresponding to actually observed mushroom intraocular melanoma.

Conclusion

A pattern of formation of intraocular mushroom-shaped tumors has been identified. According to this pattern, the initial point of their growth is always in the spherical portion, with the uveal portion forming secondarily. This pattern applies to mushroom-shaped tumors of any location and, with the exception of intraocular tumors, has never required confirmation, as it is consistent with histomorphological data. A distinctive feature of intraocular mushroom-shaped tumors is that the retinal pigment epithelium, from which they develop, unlike from many other epithelial coverings, which also serves as a source of such tumors, does not have its own stromal territory. Therefore, their growth is possible only after penetration of the choroid. This distinguishes them from fungal tumors in other locations and is one of the main reasons why their histogenetic origin was not so obvious. The discovery of this pattern, which changes existing understanding of the origin of intraocular melanoma, was made possible by an intuitive insight: a choroidal tumor cannot form a mushroom-shaped nodule. The data presented here convincingly demonstrate that this would be contrary to physical laws, not to mention the biological constraints on the growth pattern of tumors. Therefore, we are faced with the need for a fun-

damental revision of the classification and nomenclature of intraocular melanomas, which should be the next step.

Author Contributions

Artemov A.V. – conceptualization, methodology, writing, revision and editing; Kolohryvova N. M. – review and revision. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work.

Disclaimers

The authors declare that the views expressed in this article are their own and do not reflect the official position of the institutions.

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Conflict of Interest

The authors declare that they have no conflicts of interest that could bias their opinion regarding the subject matter or materials described and discussed in this manuscript.

Ethics Statements

This manuscript does not present results from studies involving human subjects and/or animals that require ethics committee approval.

Informed Consent

This study did not involve human participants, which requires informed consent for participation in the study

Data Availability Statement

Data disclosure is not applicable to this article, as no datasets were generated or analyzed during this study. All data generated or analyzed during this study are included in this published article.Data supporting the findings of this study are available from the authors upon reasonable request.

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