Tumor indiferenciado da lâmina fusca

Undifferentiated tumor of the lamina fusca

RESUMO

Na reunião da Associação Pan-americana de Patologia Oftálmica, realizada em Los Angeles CA, 10 de Outubro de 1991, no DOHENY EYE INSTITUTE, C.O. Degrazia propôs o nome de LOFONEUROGONIOMA para um tumor solitário intra-ocular, indiferenciado, originado nas células da lâmina fusca, com células indiferenciadas de expressiva diferenciação para a linhagem schwannocítica, melanocítica e neuroendócrina. Em face do trimorfismo, o patologista pode ser conduzido para os diagnósticos de melanoma, schwannoma maligno ou outro tipo de tumor. O exaustivo estudo do tumor apresentado, através da microscopia eletrônica, da histoquímica e da imunohistoquímica permitiu a formulação da seguinte hipótese: uma célula indiferenciada em repouso, a lofoneurogônia, segue as linhagens melanocítica, schwannocítica e neuroendócrina. A diversidade de células dentro de um tumor, o *continuus intratumor*, responsável pela estrutura em mosaico de muitas neoplasias, além da multiclonalidade resultante de mitoses atípicas, pode ser explicada por essa hipótese. É dessa maneira que se torna compreensível a classificação de Callender para os melanomas intra-oculares nos tipos celulares fusiforme A, fusiforme B, epitelióide, fasciculado e misto, num verdadeiro *continuus intertumores*. Para justificar a designação proposta, e para enquadrar o caso num grupo taxonômico, foram usadas duas bases classificatórias: 1º – **histogênica**, isto é, correlacionar as células do tumor com as células normalmente existentes nas membranas oculares, no caso, a lâmina fusca; 2º – **embriogênica** isto é, delimitar um grupo de tumores cuja base, no desenvolvimento do embrião, é a crista neural.

UNITERMOS: Lâmina Fusca. Tumor Indiferenciado. Lofoneurogonioma. Crista Neural. Lofoneuroepitélio de Masson.

ABSTRACT

In the meeting of the Panamerican Association of Ophtalmic Pathology, held in the Doheny Eye Institute in Los Angeles, CA on Oct 10 1991, C.O. Degrazia proposed the name LOPHONEUROGONIOMA for an undifferentiated intraocular solitary tumor, originating from the cells of the lamina fusca, with undifferentiated cells of expressive differentiation for the schwannian, melanocitic and neuroendocrine lines. Because of the trimorphism, the pathologist may be led to the diagnosis of melanoma, malignant schwannoma or other type of tumor. The exhaustive investigation of the presented tumor through electronmicroscopy, histochemistry, and immunohistochemistry allowed the formulation of the following hypothesis: an undifferentiated cell at rest, the lophoneurogonia, follows the melanocitic, schwannian, and neuroendocrine lines. The diversity of cells inside a tumor responsible for the mosaic structure of many neoplasias, besides the multiclonality resulting from atypical mitoses, can be explained by this hypothesis. This also elucidates Callender's classification of intraocular melanomas in cell types fusiform A, fusiform B, epithelioid, fasciculated and mixed, in a true intertumor continuum. In order to justify the proposed designation, and to fit the case into a taxonomic group, two classificatory bases were used: first, a histogenic one, correlating tumor cells with normally existing cells; and second, embriogenic which bases is the neural crest.

KEYWORDS: *Lamina Fusca, Undifferentiated Tumor, Lophoneurogonioma, Neural Crest, Masson's Lophoneuroepithelium.*

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AKNOWLEDGMENTS Severo Sales de Barros: Veterinarian Pathologist. Electronic Microscopy. Carlos Thadeu Cerski (Imunohistochemistry): Pathologist. Djalma Johann: Pathologist TECHINCAL SERVICES: 1 – Ocular Pathology Laboratory (Private Institution). 2 – UFRGS' Medical School's Pathological Anatomy Course Laboratory. 3 – Immunohistochemistry Laboratory of the Heitor Cirne Lima Research and Post-Graduation Center at UFCSPA. 4 – Retinal Center of Banco de Olhos Hospital of Porto Alegre, Rio Grande do Sul: complementary tests (echography, retinography).

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INTRODUCTION

Masson, (9-10) 1923, used the prefix *lophos* to designate the neural crest as lophoneuroepithelium, and the suffix *gonos* for a primitive ganglion cell,

Recebido: 11/8/2008 – Aprovado: 22/9/2008

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the sympathogonia, as well as the resulting tumors, sympathomes sympathogoniques and sympathogoniomas. (pg. 587 from the original book, and 1016 from the English translation). The designation proposed by C. O. Degrazia has the same Greek etymology:

LOPHONEUROGONIOMA from *LOPHOS* = crest; *NEURON* = nerve; *GONOS* = origin, seed and *OMA* = tumor.

The biological phenomenon is very complex and hard to be understood in all its variability degrees. That is the reason why the classifications are constantly modified. As our knowledge on the morphogenesis, cyto-secretion and immunogenic mechanisms of the living beings improves, certain aspects of the tumoral pathology become clear. The opposite is also true, because from the tumors' structure, we can infer the existence of a normal structure still unknown. In Pathology, every classification is related to the diagnosis and the prognosis. Since the first pathologists, tumors have been designated according to the similarity to the adult tissue it presents: epithelioma if it resembles the epithelium, myoma, if it resembles the muscle, etc.

Nowadays, besides the similarity parameter, which can lead to error, techniques that determine the cell specificity, as the ones in immunohistochemistry are used. However, when it comes to undifferentiated tumors, such techniques must be assessed very carefully, for cell groups with different differentiation paths can be present in the same tumor and lead to diverse diagnoses. In these cases, the merely histogenic or structural based classifications cannot clarify the tumor nature. To explain the concomitance of two different lineages of cells in a same tumor, Masson created the hypothesis according to which a Schwannocyte can be a facultative melanocyte. The exhaustive study of the presented tumor, through electronic microscopy, histochemistry and immunohistochemistry, allowed us the formulation of the following hypothesis: a non-differentiated cell at rest, the lophoneurogonia, follows the melanocytic, Schwannian and neuroendocrine lines. The diversity of cells inside a tumor, that is to say, the *continuus intratumor*, which is responsible for the mosaic structure in many neoplasias, could be explained by that hypothesis. Atypical mitosis can do that, but by other ways. Thus, Callender's classification for the intra-ocular melanomas in the fusiform A, fusiform B, epithelioid, fasciculate and mixed cell lineages, in a true *continuus intertumores*, becomes understandable. To justify the proposed designation, and to include the case in a taxonomic group, two classifying bases were used: 1st – **histogenic**, i.e., to correlate the tumor cells with the tissue normally existent in the ocular membrane, in this case, the lamina fusca; 2nd – **embryogenic**, i.e., to delimit a group of tumors which basis, in the embryo development, is the neural crest. All vascular, endothelial and mesoderm derived tumors, like the histiocytomas, etc, are out of this classification – some immunohistochemistry reations were made, like S100 Protein, lisozime, alpha1-antichymotrypsin, and Factor VIII, and outcome negatives.

One of the best ways to measure the validity of a tumors' classification is the observance of its evolution through survival statistics. That is the fundamental aspect of the classification for the uveal melanomas introduced by Callender in 1938, and corroborated in the daily praxis all over the world.

Callender's classification, limited to the histoarchitecture, nonetheless, must not work as barrier for the search for new taxonomic perspectives. The case presented by us, being a undifferentiated tumor with differential trimorphism, not allowing a placement in the architectural classification, led us to the embryogenic classification. In that classification, the central effort resides in retrace the cell transformations back to the embryonic phase.

Starting from that perspective, the choroid can be divided into three layers, which, from the inside to the outside, are: The Bruch's Membrane, the choriocapilaris, and the great vessels' layer. Between the choroid and the sclera, there is a layer interconnected with the choroid and the sclera; it is the *lamina fusca* (in Latin: *fuscus* = dark) also known as *suprachoroid*. In the artifacts produced by the manipulation, it can be detached from the other two layers,

The classical authors who deal with the eye globe morphology, place the lamina fusca either in the choroid or in the sclera, probably diverging due to the fact that fibers, cells and lamellas connect with both sides. Eugene Wolff 1948 (20) places it in the choroid, given it the synonym suprachoroid. Elise Torczinski 1992 (18) places it in the sclera, apart from the suprachoroid.

Thus, we can see that, in the lamina fusca, there are elements coming from two main origins: the mesenchyme and the neural crest. In the present work, through the immunohistochemistry and the electronic microscopy, all tumors derived from the mesoderm have been excluded, being analyzed only those derived from the neural crest

CASE REPORT

Clinical History: The patient was examined in 06/1988; visual accuracy of counting fingers from 2 meters, in the right eye, and 20/30 with correction in the left eye. At the examination, she presented scar retraction on the right face with eyelid complication and trichiasis. She had history of trichiasis' surgery in her right eye during her childhood and of extra capsular cataract in her left eye.

The pressure at both eyes was normal. At the biomicroscopy**,** she presented posterior sub-cortical and nuclear cataract. The fundoscopy was apparently normal, with visualization difficulty in the right eye due to mid´s opacity.

She was submitted to extra capsular cataract surgery, with intraocular lens implant. There were no intercurrences during the post-operatory. In 10/88 the visual accuracy was of 20/

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30, with correction, in the operated eye. The patient returned to appointment on 7/26/89, complaining about a 2-3 weeks loss of accuracy in the right eye. The visual accuracy was of 20/200. The fundus of the eye presented tumoral mass in the inferior temporal quadrant, associated to the retina's detachment that affected the macular region.

The enucleation was performed in 11/89. The patient was examined then in 1990, being asymptomatic. In 1991, however, a hepatic nodule was detected. The patient was submitted to surgery and died soon later. Autopsy was not performed.

COMPLEMENTARY TESTS

Fluorescent Retinography: Tumoral mass with little pigmentation and ruptures in the Bruch's Membrane. There are both diffusion and block areas concerning the dye. We saw no vascular net nourishing the tumor. Conclusion: compatible with amelanotic melanoma with retina invasion.

Echography: Tumoral mass with widened basis compatible with choroid melanoma.

PIECE EXAMINATION

Macroscopy: Due to the location of the tumor in the temporal quadrant, inferior and posterior, the opening of the eye was somewhat atypical, for it was intended to cut the tumor to its half. There is a slight increase in the thickness of the ocular wall, and the concave shape of the tumor is at first sight highlighted, what is unexpected for intraocular melanoma which typically possesses round or at maximum flat-round shape, always with a convex surface, nonetheless.

Microscopy: Cytology in smears, Papanicolaou Method. Many cells without visible contours, with oval or round nuclei, many of them having a *sui generis* aspect of a tie button or button (objects widely used in previous years. *Old fashioned*). No mitosis pictures were seen, generating the suspicious that the tie button shape represents amitosis pictures, but this needs further investigation.

Histology, HE: Predominantly clear vacuolized cells with oval nuclei, among which there are groups of round non-vacuolized poorly differentiated cells. There are cells forming palisades, some of which curved like a migratory birds flight, or paraglider. In the tumor, one can observe the almost inexistence of vascular bed and stroma. There are ruptures in the Bruch's membrane with tumoral cells invasion, what also occurs in the walls of a vessel. The lamina fusca, observed some centimeters before the tumor, starts to become thicker and thicker, until it continues directly with the tumor.

In the sclera, a ciliary nerve presents Schwannian cells hyperplasia. A nerve that runs in parallel with the lamina fusca highlights the morphological differences between the two tissues.

The vacuolized aspect of the cells, seen with routine coloration (HE), shows they secrete soluble substances, lipoid or proteoglican, a mucoprotein. Unsoluble aggregates probably are ceroids.

In the original tumor, with histochemistry, immunohistochemistry and electronic microscopy techniques, positive fields for melanocytic, Schwannian and neuroendocrine cells were found.

In the metastases, the aspects are as varied as they are in the original tumor.

COMMENTS

Since we are dealing with a probably still not described tumor, with a unexpected locatio, and with non-consensual diagnnosis among pathologists, we are searching for a classification to include it. To achieve that, we have made reviews on schwannomas, melanomas, the uveal normal histology, its embryogenesis and the fundamentals of the intraocular tumors' classifications, especially the Callender's (4). From the very beginning, two points have called our attention: the relevant participation of the neural crest on the uvea's constitution, and the classification (proposed by R.P. Bollande (2), in 1974) of the diseases originated from anomalies of the neural crest, or from its derivatives. He called such diseases neurocristopaties. He included the neuroblastoma, the disease of Von Recklinghausen, the pheochromocytoma, the carcinoid, the neurocutaneous melanosis, among others. The *melanosis oculii* and the nevus of Ota, that have not been mentioned, hould be included.

Classifications have been proposed based on the secretions produced by the neoplasias, but as they cannot be used by oncologists for they do not provide prognostic indications, they must be abandoned. Moreover, let us take a neoplasia secreting more than one substance. How would we name it? We have the examples of the APUDomas – from the acronym: Precursor Uptake Aminocid Decarboxilation – the Fibronectoma, the Calcitoninoma, and so on. We must admit an exception, at least for a while, for the melanomas whose cells secret melanin.

EMBRYOGENESIS – Since the pioneer works, among which we highlight Sven Hörstadius' (7), (1947-1950), it is known that the neural crest originates many structures of the adult, including the cells that bear pigment, the melanocytes. After the first description, made by Wilhelm Hiss (1869) (17), there were studies whose history was complimented by the following words by Hörstadius:

"It is amazing to follow the thought lines and the methods used by the experimental embryologists, as an attempt to clarify not only the structures deriving from it, but also its properties."

The melanins, existent in the hair, and different parts of the skin and in the eyes, besides its main function as defense to the UV rays, perform, in the eyes, other functions. In the brain, they are located in the *nigra* substance, where they have influence over Parkinson's disease. In the last decade, with the development of the genetics and the immunohistochemistry,

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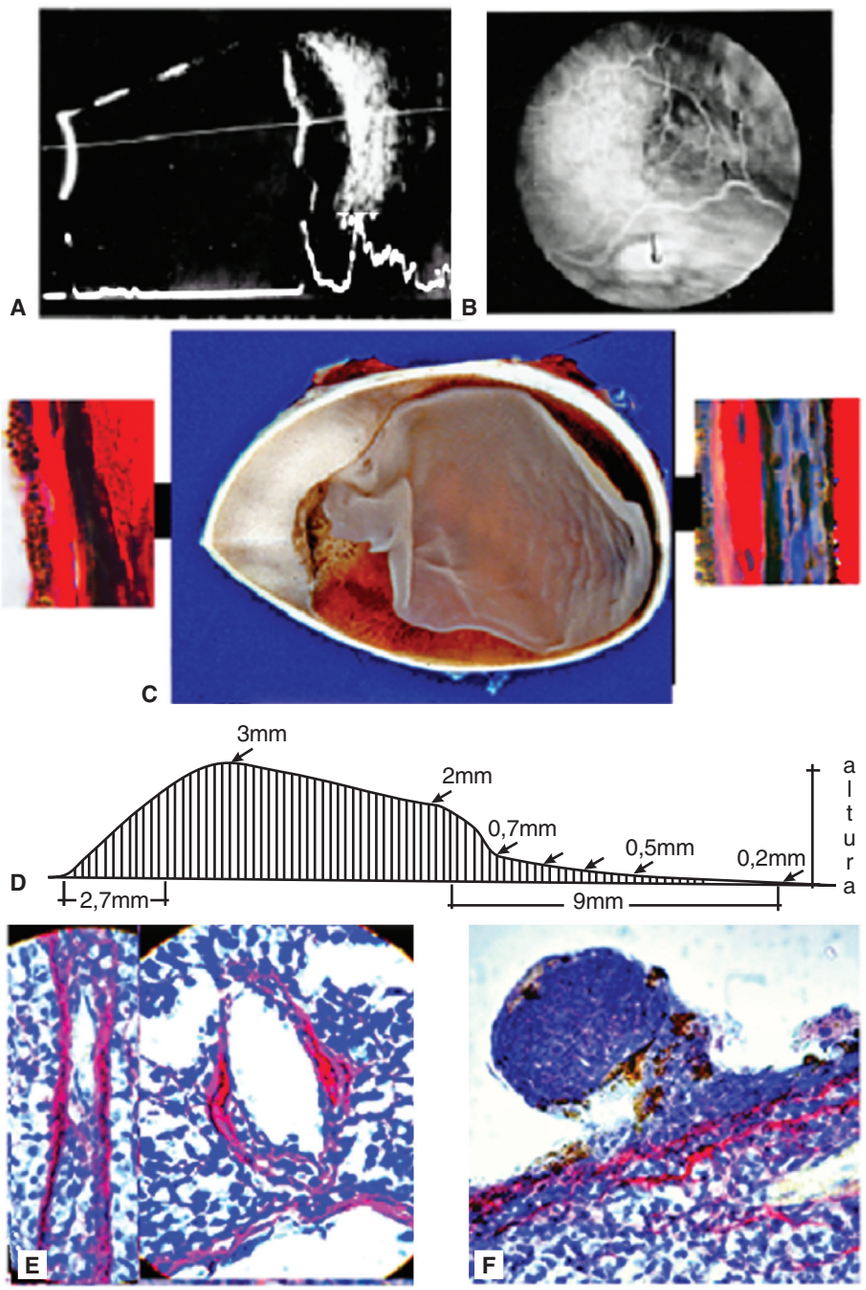


Figure 1 – Image displayed anatomo-clinical correlation.

A. The echography reveals a widened-basis neoplasia.

B. The first sentence in the fluorescent retinography medical report can be confirmed by the examination of the piece that shows a whitish color. The rupture of Bruch's Membrane is evident in the image f, in a cut of the concave part with 40 x augmentation. The Picro Syrius coloration shows the membrane's disjunction by the invasion of the tumoral cells that, projecting to the vitreous obtains polypoid aspect. Such tumoral polyp is involved by pigmentary epithelium cells, corresponding to the brown points of the concave surface.

C. The ocular globe, adequately cut in order to allow tri-dimensional visualization of the neoplasia, measures 25mm in the Antero posterior way and 23mm in the equatorial way; it presents a whitish tumor 3 to 4mm height, and with 15mm x 7mm on its basis. The height stays more or less constant, giving the tumor's internal face a concave shape. One can observe regmatogenous detachment of the retina and slight thickening of the sclera.

Two segments of the LF are symbolically placed side by side, the one to the left, with normal thickness; the other, to the right, with enlarged thickness.

D. Approximate Graph, made with the naked eye, of the progressive thickening of the LF, next to the tumor.

E. Histological cut, colored by Picro Sirius, showing two vascular beds covered with tumoral cells. The fibrous laminas that involve them continue with Bruch's Membrane. The empty spaces probably are produced by contrast's extravazation. Augmentation: 40x.

F. In this cut, the Bruch's membrane is disjointed by the tumoral cells crossing, and cells that aggregate in a polypoid shape projecting themselves to the vitreous. Coloration by Picro Sirius. Augmentation 40x.

great part of the works focuses especially on the melanoblasts's migration mechanisms. The melanoblasts are cells deprived of pigment, precursor to the melanocytes. The complexity revealed by those researches can be seen in the mere fact of the codification of the genes implied in the mutations that make the melanoblasts settle and give the mice hair color; they are around 90 (6). On the other hand, the precursor cell finds environments with the most varied substances in its trajectory from the neural crest to its destination. Such substances do not change by chance, but are influenced by another gene's chain in its formative waterfalling-like movement. In the case displayed, the melanoblast finds an environment rich in tyrosine, and through a signalization, a protein, tyrosinase, triggers a series of transformations that, passing by substances called indoles, form the eumelanin or the neuromelanin. Therefore, there are three elements capable of being influenced in the mere migration of a cell: the genetic mechanisms, the signalization and the transcription.

This overall review was necessary for the understanding of the

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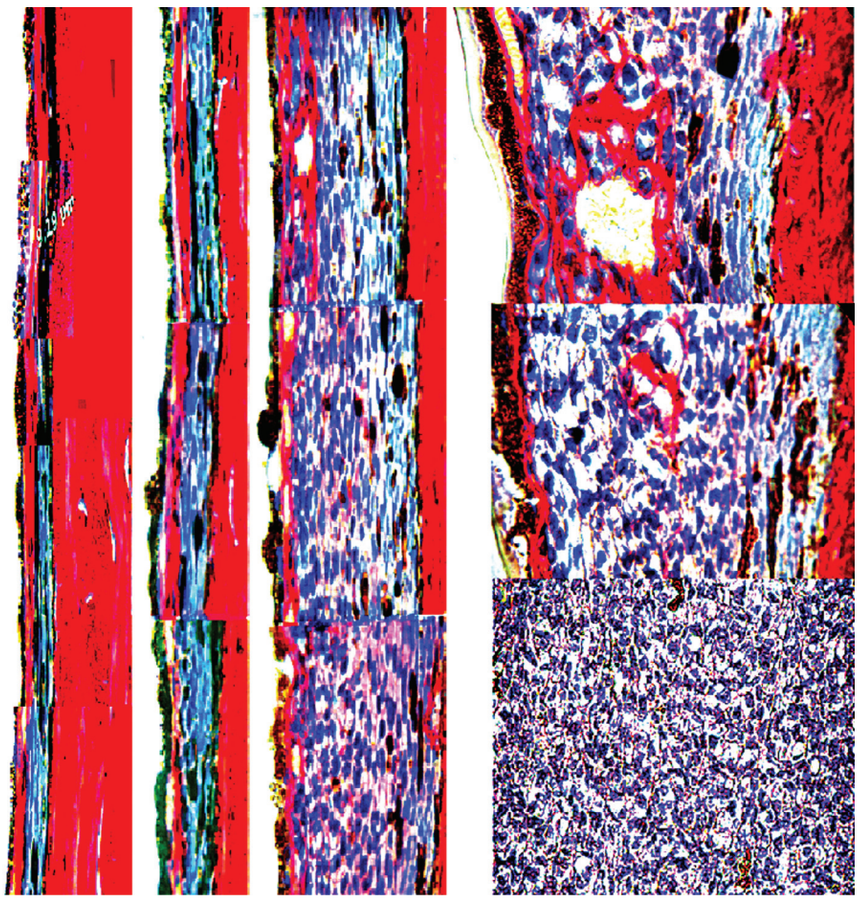


Figure 2 – Progressive hyperplasia of the lamina fusca and tumor.
The four columns are composed by segments of the LF sampled a certain distance from the tumor. The examination of the board must be performed top bottom and from the left to the right. The progressive thickness' augmentation caused by cell proliferation accentuated near the tumor is evident. Signals of malignancy start to come up in the third column already, superior segment, with an invasion of a uveal vessel, and in the inferior segment, by the formation of palisades, like migrant birds' flight or paragliders. That palisade disposition translates the ordination of the embryonic epiblast's cells, which means non-differentiation, a strong signal of malignancy. The invasion of the uveal vessels' walls is evident in the fourth column, where a vessel in the second meridian has its light almost obliterated. Finally, the LF's cell proliferation expands in the tumor, seen in the inferior segment.

lophoneurogonioma's formation mechanisms. The Fig. 7 and the following scheme firstly indicate that the main support is the morphologic one. This is how the neural crest's cells, are compared to the tumor's non-differentiated cells, and the palisades existent in the epiblast, are compared to the tumor's palisade – The first pathologists used to compare them to a kind of candy called *bala de estalo*, a caramel whose wrapping paper had fringes at both extremities. Our comparison to migratory birds' flight or paraglider better.

HISTOPHYSIOLOGY – Some studies suggest the cells originated in the neuroectoderma are programmed to have a neuroendocrine function. Thus, positive reactions for Chromogranin A in tumors derived from the neural crest are not surprising, as in the case shown on Fig. **5h.** The final phenotype evidently depends on the genetic equipment brought by the cell and on the environment it is living in.

The lamina fusca is, among the ocular membranes, the almost pure depositary of the cells migrating from the neural crest (NC), for it has no own vessels, nor nerves, only conjunctive lamellas whose evolving derivation has not been studied. They are quiescent cells capable of transformation. How can we understand such capacity? Burns et al. (3) highlight the Bagnara's hypothesis, according to which a certain number of cells of the NC's lineage retains in their genome the capacity of forming pigment from a primordial pigmentary organelle. That would explain why different tumors are pigmented. It is possible to admit the idea of a gene repressed in the evolutionary process, which would suffer derepression due to factors resulting from the host's inner environment – the internal or intratumoral environment. Berger and Masson, 1923 (13) described a uveal ganglioneuroma case, in which nerve plexuses, schwannian cells, ganglion cells, melanoblasts and tactile corpuscles were found. That was the starting point for Masson's hypothesis (11-12), about the possibility of the Schwann cell to transform in a melanocyte.

GENETICS – Concerning the hypothesis of the neural crest primitive cell's specificity, which, in this work, C. O. Degrazia proposed to call lophoneurogonia, three hypothesis are presented by Drew M. Noden, (14, pg. 113): 1 – mosaicism, a heterogeneous population brings, from the beginning, a determined differential path for each unit, independently from the influence of the tissues crossed by during the migration. 2 – Subpopulations' limited groups with evolution programmed for the group, also independent from the environment. 3 – Neural crest cells' equipotentiality, the differentiation being made during the migratory path, by environmental influence.

Current studies have been shown that the 3rd hypothesis is the most suitable, corroborating old works by Spemann (17) who demonstrated the influence of elements present in the tissular environments in the differentiation of embryonic tissues transplanted

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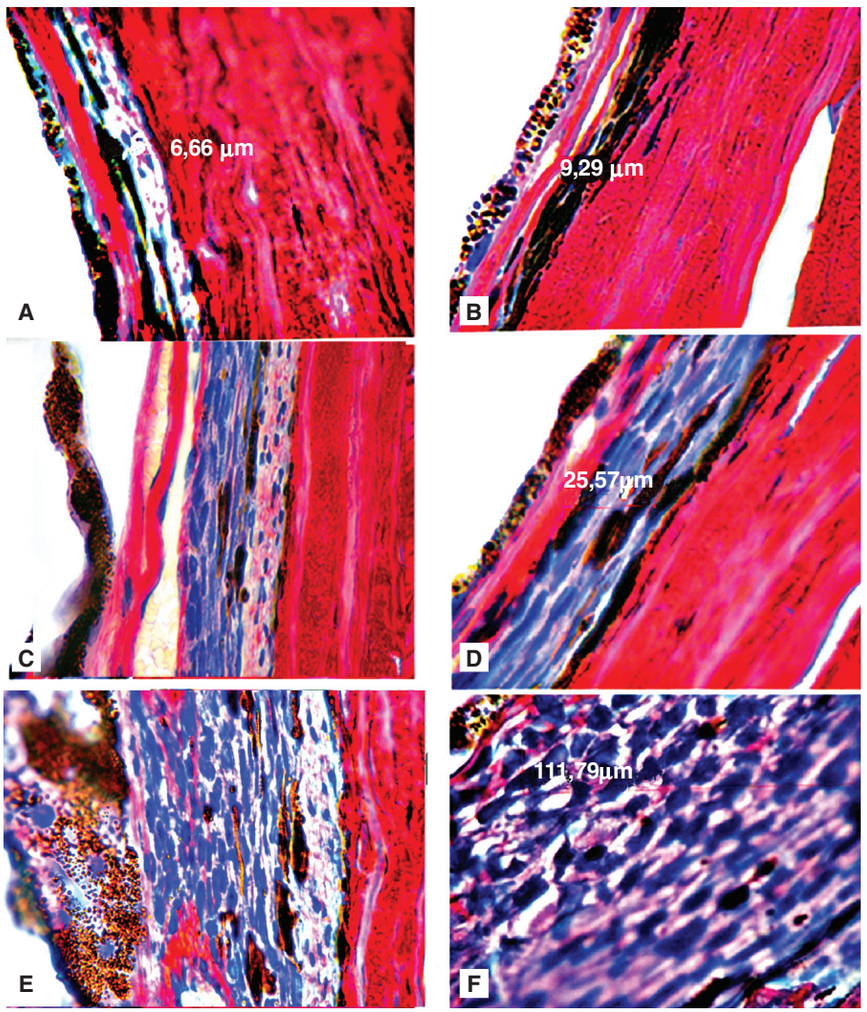


Figure 3 – Precise measurements. relation between lamina fusca, choroid and nerve.
The measurements were made with software Axion Vision by Zeiss, and vary from 6-9 µm, 118 µm, and more, being the smaller the one beside a nerve that runs parallel.
A-C-E. In this column, one can observe a nerve that, running parallel to the LF, maintains the same thickness during all its trajectory. The LF on the contrary, has its thickness gradually enlarged. That very nerve penetrates in its entire trajectory are salient and penetrate the tumor where, with HMB 45 made immunohistochemical reaction, they can simulate a melanoma. See, on Fig. 5, the nerve accompanied with/by the immunohistochemical reactions. Melanocytes also accompany the LF in its whole extension.
In picture **e** there is a conglomerate of pigmentary epithelium cells.
B-D-F. In this column, exact measurements were made with software by Zeiss. In b, 9,29; µm, in d, 25,57 µm; and 111,79 µm. in **f;** a flat cell from the pigmentary epithelium measures 10 µm.
One can observe the choroid only starts to be invaded by tumoral cells while it approximates the tumor.

to ectopic regions. He called these elements organizers. Waddington (19, pg. 5's) – from whom we extracted the quotation – says what follows:

"The genes cannot be observed as immediately effective as causes to successive differentiation processes, though they unmistakably are the fundamental elements that, at the end of the day, control them."

These old ideas – Spemann's works date from 1918 and Waddington's book was edited in 1947 – have at the present days full confirmation with the studies on stem cells. Actually, the lophoneurogonias are authentic embryonic stem cells, totipotent, suffering differentiation in their migratory path. The tumor we presented, and named lophoneurogonioma, is formed by these cells and, since they are located in the lamina fusca, that shares the destination for the sight with other structures of the eye, therefore suffering light influence, differentiate into Schwannoblastic and melanoblastic lineages. They have, however, other abilities, as the neuroendocrine function and, due to the numerous clear vacuolized cells, synthesis of the substances soluble in the normal histological processing.

PATHOPHYSIOLOGY – The expression *uveal melanocytes,* evidently embraces a spectrum of *gen/phen* cell types – term utilized by C.O.D. to indicate they are genotypically and phenotypically stabilized cells. Just like the mosaic structure, inside a tumor, reveals the *continuum cellularis intratumor,* the several kinds of melanoma, fusiform A, fusiform B, epithelioid, fasciculate and mixed, constitute a *continuum cellularis intertumores,* for all their cells have the same embryogenic derivation. Romsdahal and Cox's work (15) is important to justify Callender's classification – that presupposes clonicity, that is to say, specificity. They studied, in culture environment, cells taken from a melanoma with varied cell morphology, polyhedral, fusiform, cuboid, and great cuboid. During their propagation in the culture, all these lines surprisingly kept the same morphological standard, pigmentation and chromosomal characteristics. The pigmentation degree varied in the different lineages, being more intense for the polydendritic This work is a valu-

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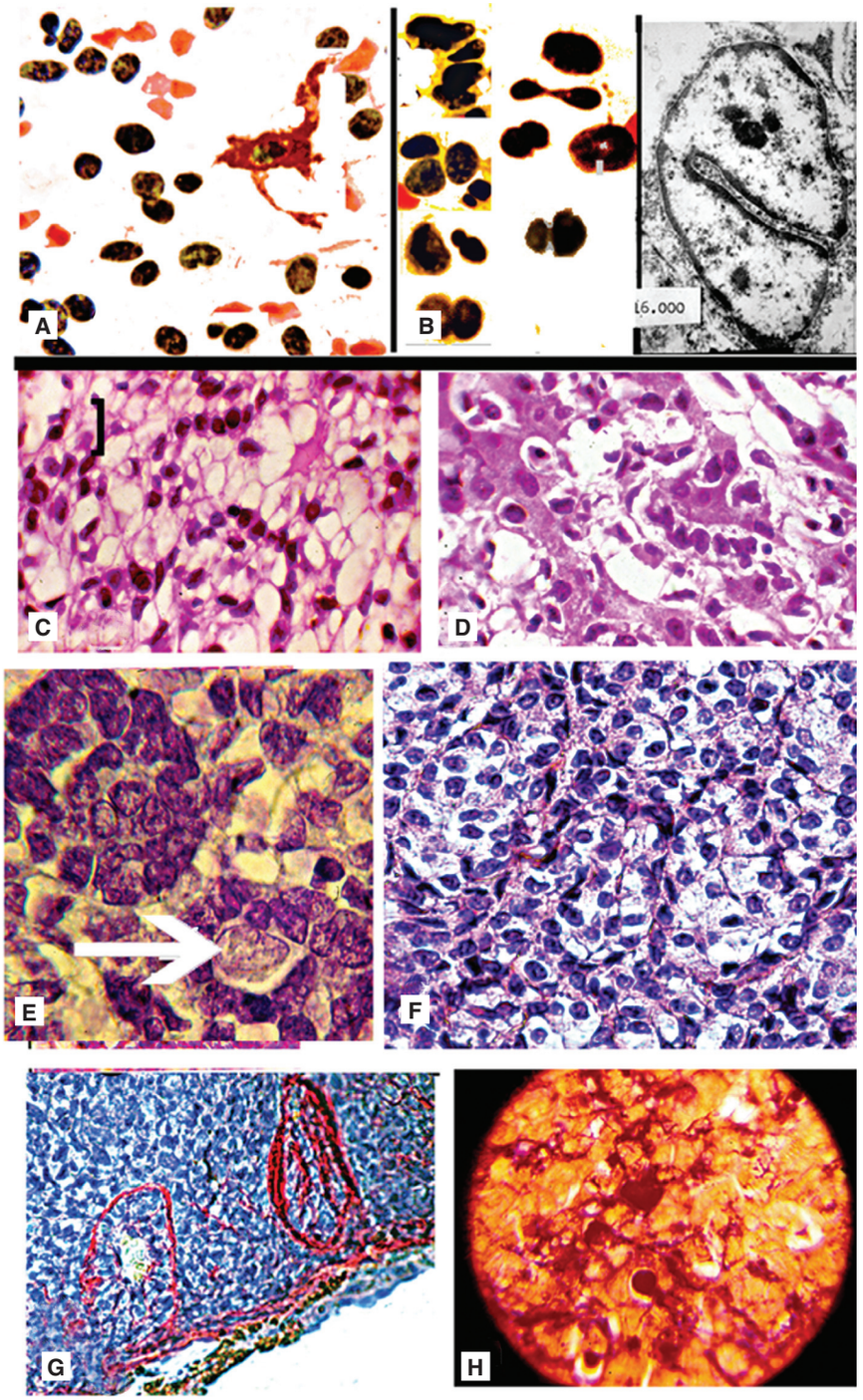


Figure 4 – CITOLOGY AND HISTOLOGY
The figures at the heading are aimed to compare the cells obtained by smear, with 100x augmentation, presenting an aspect similar to buttons or tie button (old fashion), with another having an 16,000x augmentation, obtained by electronic microscopy, presenting accentuated fold, almost dividing the nucleus in two parts.

A-B. Cytology in smear, in which one can notice round or slightly oval hyperchromatic nuclei, some of them with folds that make them similar to tie buttons. The cytoplasm is scarce, or not seen. In **a,** one can see a melanocyte. In **b**, nuclei in palisade. Coloration: Papanicolaou Method. Augmentation. 100x

C. Clear undifferentiated cells; two typical arrangements of migratory birds´ flight. HE coloration. 100x augmentation.

D. A large cell originating palisades; in the superior portion there are two cells; in the inferior, five. HE coloration. 100x augmentation.

E. Undifferentiated cells, with glandular structure. Inside one of them, the arrow indicates secretion insoluble to the techniques used, like in a ceroid compound. HE coloration. 100x augmentation.

F. Clear cells, with large round or slightly oval nuclei, with arrangement compatible with neuroendocrine tumor. HE coloration. 100x augmentation.

G. Vascular channels, completely covered by tumoral cells. The conjunctive wall derives from Bruch's Membrane. Coloration: Picro Syrius. 20x augmentation.

H. Secretion globules, from which come membranoid stripes. Histochemistry. Lilie Method.

The Lilie Method, referred here, was published as Lillie´s Performic or Peracetic Acid Schiff Reaction, in LILLIE, R.D. Histopathology Technique and Practical Histochemistry The Blakiston Company, Inc.. New York, Toronto. 1954. (page.310).

able support for the hypothesis that each cell type of the uvea and of the tumors they form, belong to a defined clone.

MALIGNANCY GRADUATION – The neuroendocrine tumor does not escape the graduation established for tumors in general, based on the differentiation degree: the more undifferentiated, the more malignant and more radio sensitive. There are, nonetheless, among the well differentiated tumors, groups that behave with malignant character, capable of invasion and metastasis. In these cases, are used the criteria of seize, >2cm, necrosis areas, atypisms, higher number of mitosis, >2 in ten microscopic fields seen with great augmentation, accumulation of protein p53, lost of immunoreactivity for chromogranin A**,**. and argyrophile. This

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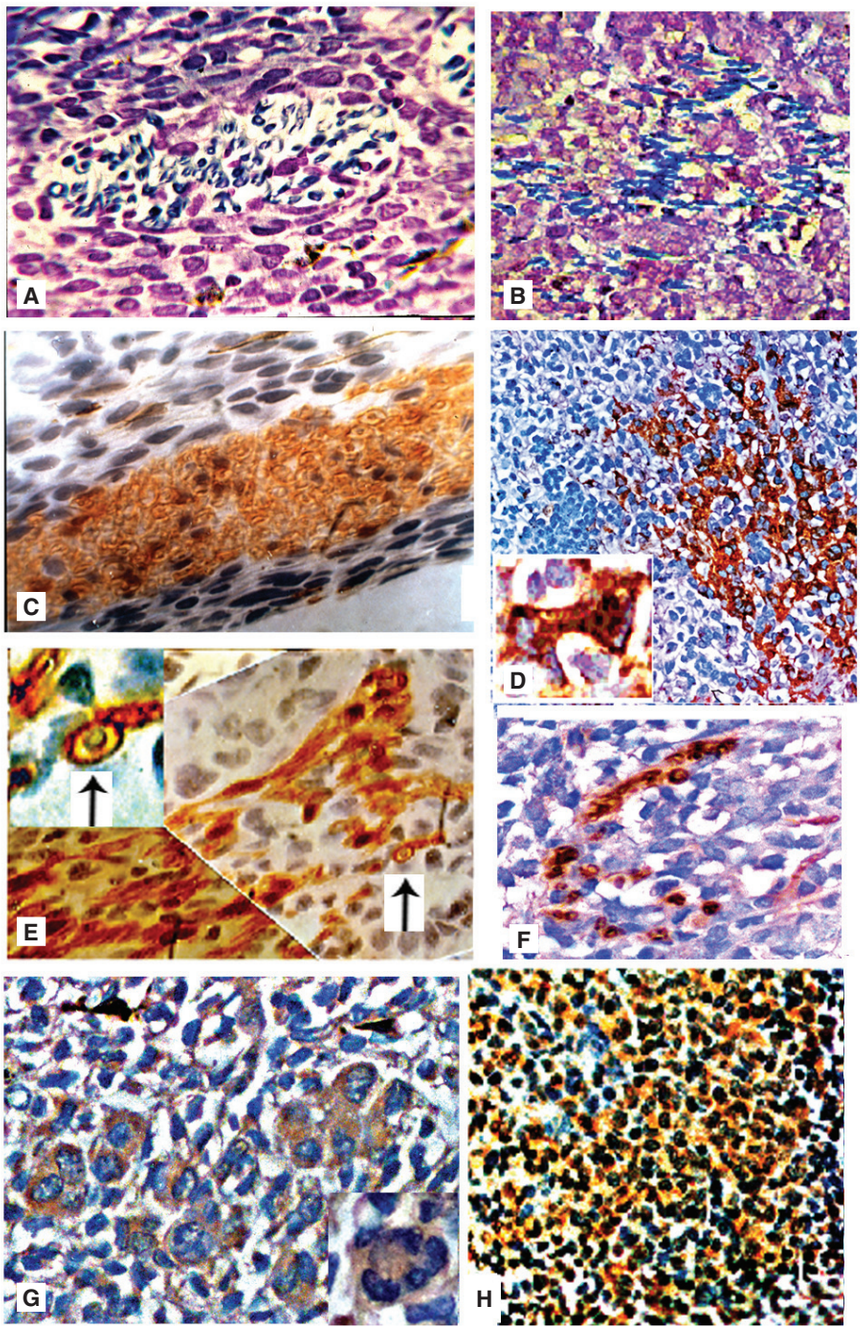


Figure 5 – Immunohistochemistry and histochemistry.
The first pictures are taken from a nerve lateral to the LF and penetrates the tumor.

A. Cut of the nerve next to the tumor. One can notice the incipient invasion of malignant cells. Coloration by Luxol.

B. Nerve already inside the tumor, with massive invasion, the nervous fillets becoming apart as in an explosion. Coloration by Luxol.

C– E. The same nerve treated by the reaction of the Protein S-100. In **e,** in the superior insert, a transversionally cut axon, showing the axle cylinder and the myelin sheath. The arrows are correlated, indicating the axon location.

D. Group of melanoblasts among extensive negative areas. Reaction by HMB-45. 20x augmentation. In the insert one can see a widely enlarged melanocyte. 40x augmentation.

F. Reaction by PBM for peripheral myelin. 40x augmentation. It is the same nerve whose sheaths are dissociated because of the cells' invasion. .

G. Groups positive for PBM, indicating differentiation for Schwannian cells, which form syncytiums. There is a positive multinucleated cell, similar to the epithelioid cells found in the epithelioid melanomas. 40x augmentation.

H. Group of cells positive for Chromogranin A. They are cells that differentiate to neuroendocrine tumor. 20x augmentation.

list is displayed in the release of works presented on the 8th European Union Gastroenterology Week, made by Rudolph Arnold (1).

LOPHONEUROGONIOMA'S MALIGNANCY – The only case found revealed high degree of malignancy, with hepatic metastasis followed by death soon after. The microscopic fields did not present mitosis, but the cytology revealed nuclear folds. The differentiated areas presented immunoreactivity for melanin, gliofibril and crhomogranin A. Moreover, the great extension of empty cells, denoting secretion accumulation, showed inhibitor enzymes deficiency.

LOPHONEUROGONIOMA CATEGORIZATION – According to a critical publication made by Rudolph Arnold, the designation neuroendocrine tumor is considered more appropriate to replace current expressions such as neuroendocrine carcinoma, carcinoid, APUD-oma, etc., for al those derive from the diffuse neuroendocrine system. Most of the reports referring to this system are about tumor of the pancreas, the digestive tract's mucosa – with 15 different types of endocrine

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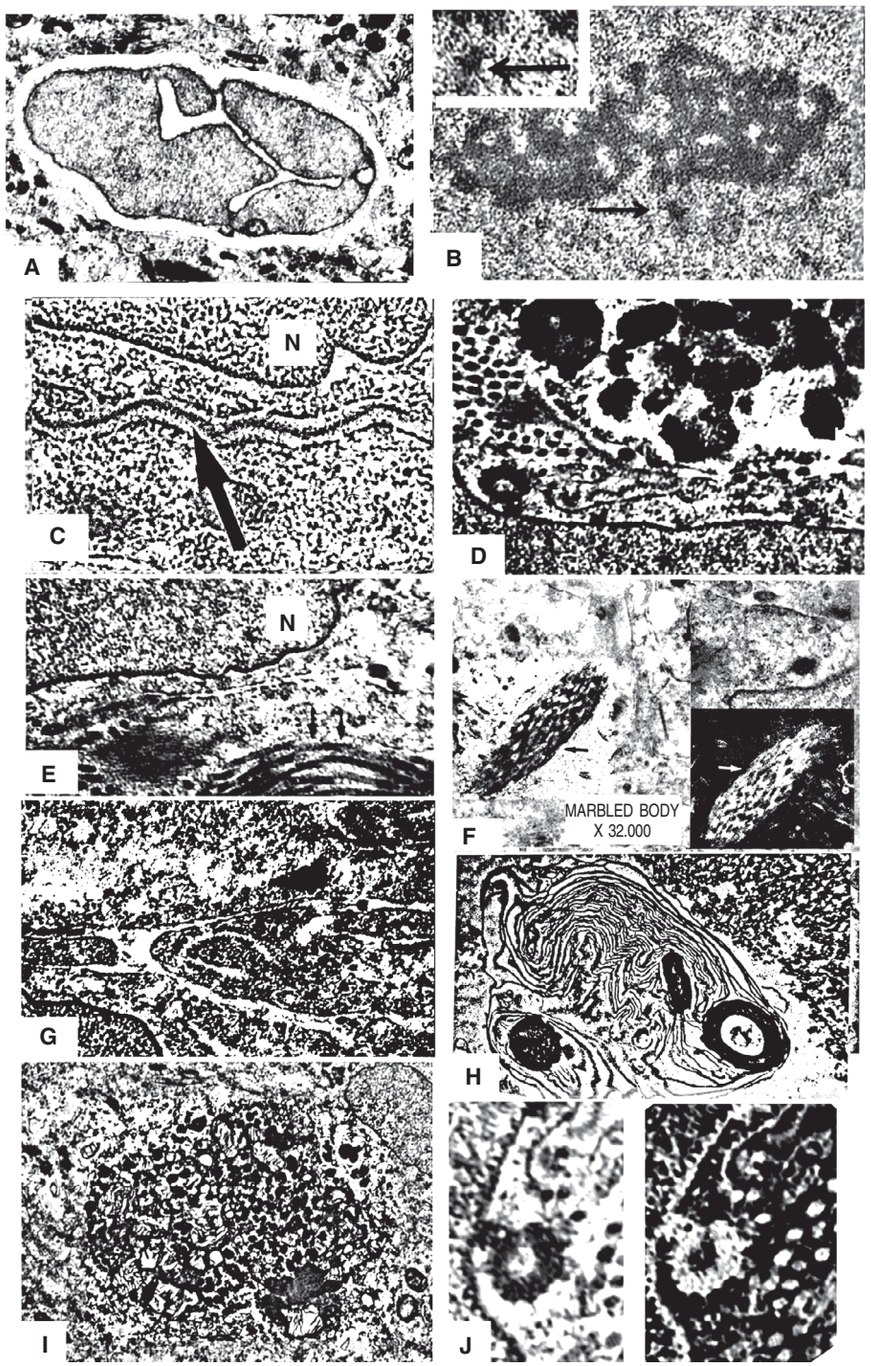


Figure 6 – Electronic microscopy. With the contribution of Severo Sales de Barros. The aspects found are widely varied. We present those of them that can lead to a diagnosis of malignant Schwanoma. Techniques performed from paraffin blocks and initial fixation in buffer formol.

- **A.** Cell with multilobulated nucleus. There are lobules fixed practically only by the nuclear membrane. Nucleoli are not seen. The clear halo around the nucleus has been artificially made, to emphasize the lobulation.
- **B.** Large and irregular nucleolus, with nucleoplasma invaginations, with some detached parts. The insert shows the detached part with more details. Augmentation 10,000x and enlargement by computer.
- **C.** The arrow indicates incomplete basal membrane.
- **D.** Interstitial membranes coming from the matrix of a fundamental substance. Transversionally cut collagenous fibers, and eletrodense granules. .
- **E.** Longwise cut collagenous fibers.
- **F.** Structure approximately similar to Luse bodies, denominated here as marble body). Beside, a representation using computer inversion filter. Augmentation: 32,000x.
- **G.** Digitations...
- **H.** Myelin membranes.
- **I.** Compatible with lysossomic vesicule full of myelin membranes and melanossomes.
- **J.** Evagination of the nuclear membrane in a ring shape. Beside, with computer inversion filter. Compare to the same aspect of the marble body.

cells, producing hormonal peptides and/or biogenic amines – and other sites where there are disperse neuroendocrine cells, like thyroid, lungs, biliary tree and urogenital tract. We can see, through this review, that the eye globe is not a site considered to shelter neuroendocrine cells – only the metastasis of such tumors are described in the eye. In order to differentiate the tumors previously presented by us, it is fair to use the proposed designation of *Lophoneurogonioma*.

LOPHONEUROGONIOMA'S SITE – Since it is a primitive tumor of the eye globe, it is necessary to know its location. Measurements on the LF progressive hyperplasia with common ruler with the naked eye were made, as we can see in the graphic in Fig. 1 d. In the microscopy, the Fig. 2 shows the progressive thickening of the lamina fusca, and its continuity with the tumor. On the Figs. 2 and 3, rigorous measurements of the lamina fusca were made by using the software Axion Vision, by Zeiss.

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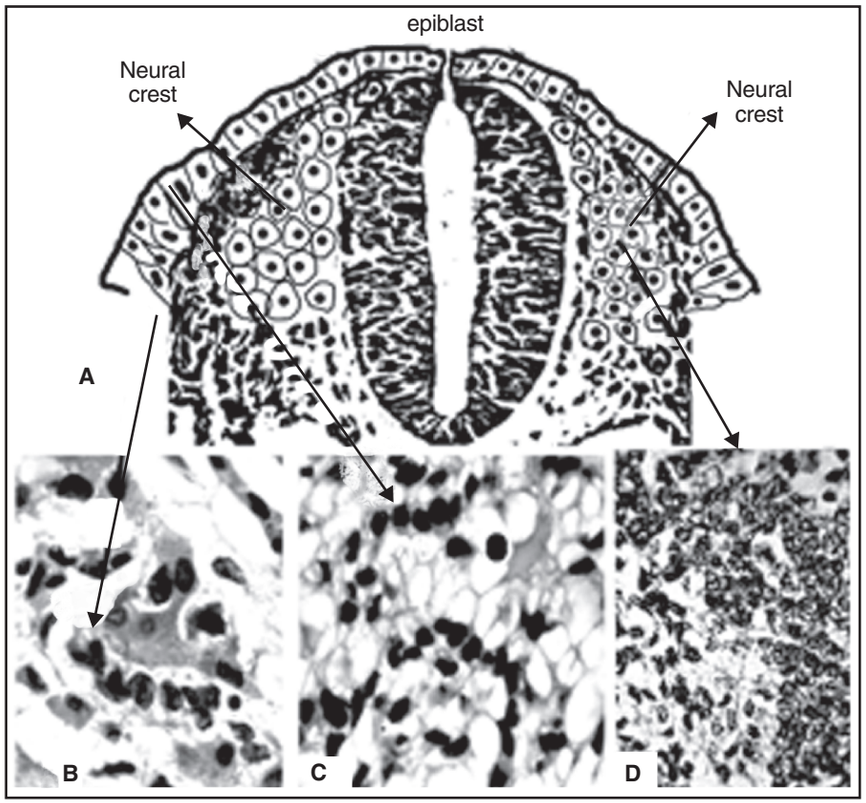


Figure 7 – Embryogenic correlation.
A. Semi-schematic picture, based on mouse embryo to highlight the epiblast and the neural crest. From the fold that unite the epiblast and the neural tube, comes out, like in a blooming, the neural crest, also called ganglionar crest. The NC involves the neural tube on both sides.
B. An epithelioid cell originating two lines of cells, one of them (superior) containing two cells; the other (inferior), with more than six.
C. Two curve palisades with configuration of migratory birds' flight or paragliders.
D. Groups of undifferentiated cells, with structure much similar to the one in the neural crest's cells, or lophoneurogonias.
NOTE: The arrows show the correlation. The curve palisades may reveal a genetic tendency originated from the epiblast, which has to curve during the act of cover the embryo.

ANATHOMICAL CLINICAL CORRELATION – Up to this moment, the LF has not been considered site for tumors. For the case presented here, both the Fluorescent Retinography and the Echography suggested compatibility with choroid melanoma, and the patient was submitted to enucleation with that diagnosis. We think the LF's thickening causes difficulty for its clear observation. Other processes like agenesis, hypoplasia, infections, and other defaults associated to other diseases have not been reported so far. Hyperplasia and tumor have been presented, by first time, with this case.

SUMMARY

The tumor reported is the casual discovery of a neoplasia formed by neural crest's primitive cells, quiescent in the lamina fusca, offering a rare opportunity to validate the 3rd hypothesis, the equipotentiality with differentiation by environmental induction.

An embryonic classification for the tumors of the uvea and the lamina fusca must start from the epiblast, the neural crest derives from, the skull's mesoderm and mesenchyme. The latter are going to originate osseous, cartilaginous, muscular, endothelial, histiocytic, etc. tumors, that is to say, the different kinds of sarcomas. The NC, on the other hand, is going to originate melanomas, schwannomas and neuroendocrine tumors.

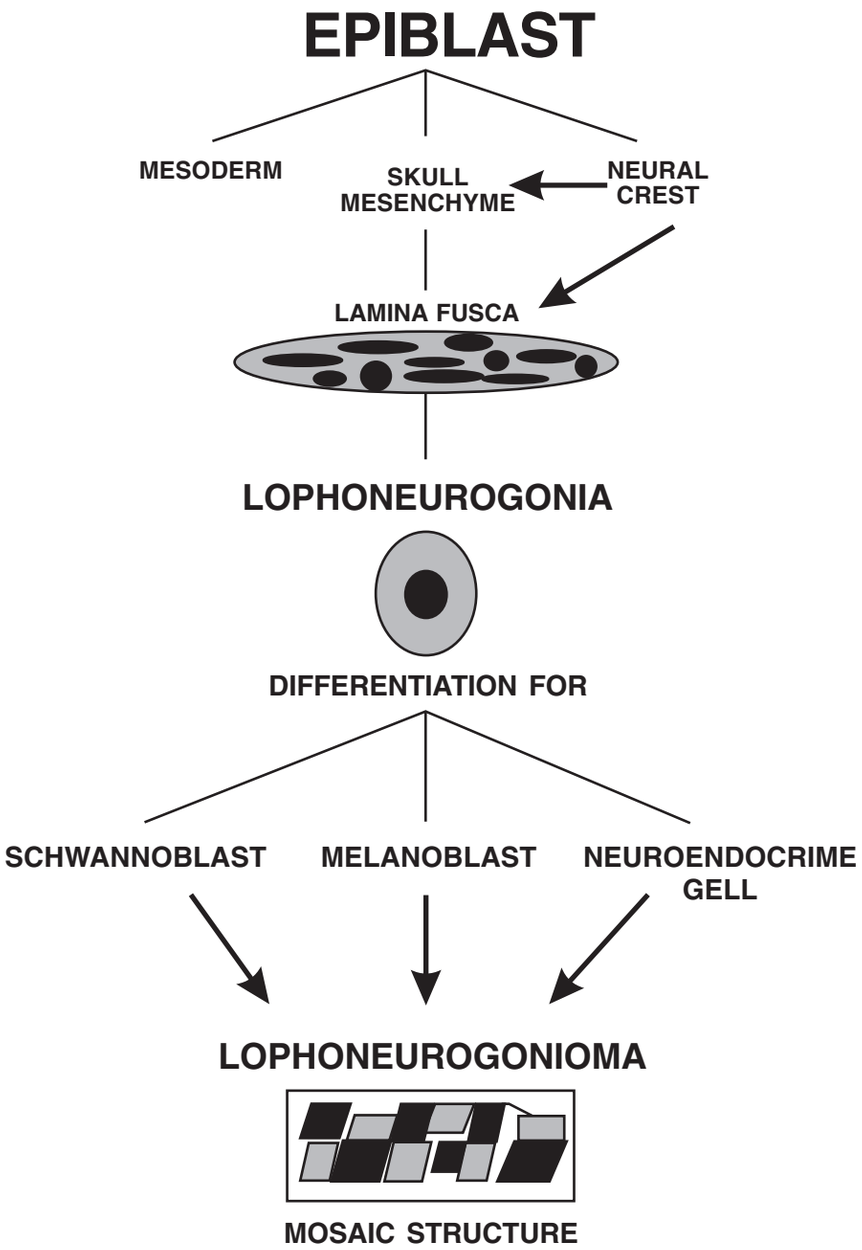
The curved palisades' aspect seen in the histological cuts must be compared to the Fig. 7, in which we see the epiblast tendency to curve.

DISCUSSION

The tumor's histological examination reveal that it unmistakably is a undifferentiated neoplasia, presenting suggestive areas for melanoma, schwannoma and neuroendocrine tumor, making diverging diagnosis possible. The schwannoblastic aspect has been documented by the immunohistochemistry and electron microscopy's techniques. The immunological reactions for melanin and neuroendocrine secretion (chromogranin A) confirm the lineages for melanoma and neuroendocrine tumor.

For the cells to form a tumor, it is a primordial condition that they are free to move around. By that reason, we admit three types of Schwannian cells: *anchored* in the axon, (also called sedentary by the scientific literature) in which they wrap up forming the myelin sheaths, being, therefore, fixed; *migratory* that, depending on the differentiation degree, can produce or not produce myelin, being free and mobile; and the *melanogenic*, responsible for the pigmentation on the pigmentary schwannoma tumors or in the normal tissues. Structural differences between these types have been reported; we emphasize the following common characteristics: sliding arms, as they were long pseudopods, incomplete basement membrane, usually linked to amorphic protein accumulations, formation of collagenous fibers, and, depending on the differentiation or external stimuli degree, several types of secretion. Concerning the nucleus, the presence of folds sometimes so deep that can reach the nuclear membrane, is distinctive. When tumors are formed, the presence of wide stripes collagen, sha-

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In the scheme we have represented the paths of cells' transformations, from the epiblast until the neoplasia's formation. The three lineages we were able to determine with histochemical and immunohistochemical methods and with electronic microscopy are present.
The cells are derived from the neural crest, which is formed in the junction of the epiblast that involves the embryo and the neural tube. They remain quiescent, i.e., sleeping, in adults. In the dorsal and ventral regions, the NC originates the ganglionar chain, which is why it is also called ganglionar crest. In the inferior part of the scheme we have the word mosaic structure, indicating that the lophoneurogonioma is formed by three cell's clones.

ped in small fuse ending in point, the Luse's bodies (8), and other types of anomalous collagen, has been considered pathognomonic.

Those considerations result from the observation of the images.

On **Fig. 1c**, the macroscopy shows a concave tumor, obeying the sclera's curvature, and the lamina fusca's thickness gradually increasing. On **Fig. 3 a,c,e,** a parallel ciliary nerve shows the morphological and tinctorial differences with the LF's cells. On **Fig. 1 f**, we can see the Bruch's membranes' crossing by tumoral cells with polypoid projection in the vitreous. In the nerve/tumor relation, all techniques show independence between them, the nerve penetrates the tumor without contributing to its formation. The correspondence between the coloration by luxol, for the myelin basic protein (MBP) and the protein S-100 is evident on the images. With this last reaction, **Fig. 5 e,** is very appealing, for it shows an axon transversally cut and surrounded by the myelin sheath. This picture is rich in information. It shows the insinuating capacity the non-differentiated cell has to produce several kinds of secretion: the neuroendocrine, the melanogenesis, the myelinogenesis and the fibrilogenesis. Schwannian cells and melanocytes are seen. **Fig. 4 c,d** shows the curved palisades, like migratory birds' flight or paraglider, the cells showing close similarity to the neural crest's primitive cells. The colorations by PAS, the **t**oluidin blue and the Lilie method for basal membrane show deposits of substances compatible with mucoproteins. On **Fig. 4,** top right, is a cell seen with electronic microscopy presenting a fold, what explains the unexpected aspects mentioned on the cytology in smears harvested by puncture before the piece's fixation. The numerous cells with nuclei with tie button form call the attention. The comparison of these cells to the schwannomas' ones in electronic microscopy explains the uncommon aspect: the nuclei can present deep folds, being fixed only by the nuclear membrane. The fission becomes easy, like amitosis' pictures. The electronic microscopy, on **Fig. 6**, shows the elements that can characterize the Schwannian cells, in the schwannomas; the Luses' bodies call the attention. The collagen's accumulations with external membranes and incomplete basement membrane, and long processes or sliding arms, are part of the picture.

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In order to answer whether the neoplastic cells come from the nerve or from the lamina fusca, the observation of the **Fig. 5** is decisive. In **Fig. 3. a,c,e** and **Fig. 5 a,b,c,d,e,f,** we can see, through histochemical and immunohistochemical methods that the nerve penetrates the tumor's body passively, being invaded, as it goes deeper, by tumoral cells; its myelin sheaths are progressively separated one from the other, to the point it gives us the idea of an explosion. Therefore, the neoplastic cells do not derive from the nerve.

CONCLUSION

All documents presented clearly indicate that it is a undifferentiated tumor, originated from the lamina fusca, formed by cells derived from the neural crest and from the neuroepithelium, with capacity for differentiation into schwannoblastic, melanoblastic and neuroendocrine lineages. Since we have not found any reference to this tumor – and to its location in the lamina fusca – in the consulted literature, C.O.D. have proposed it the name of lophoneurogonioma, from *LOPHOS* = crest, *NEURON* = nerve, *GONOS* = origin, seed and *OMA* = tumor, separating it from the tumors of the digestive tract and of other sites, where they are called neuroendocrine tumors.

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