Primitive tumor of lamina fusca Original findings

Tumor primitivo de lâmina fusca Achados originais

Carlos Oswaldo Degrazia[1]

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 intraocular, indiferenciado, originado nas células da lâmina fusca, com células indiferenciadas de expressiva diferenciação para a linhagem schwannoblástica, melanoblástica e neuroendócrina. Em face do trimorfismo, o patologista pode ser conduzido para os diagnósticos de melanoma, schwannoma malignos, ou tumor de células endócrinas. Foi feita após essa data uma publicação na Revista da AMRIGS. Porto Alegre, 52 (4): 261-272, out.-dez 2008, na qual consta a lista dos colaboradores. A publicação atual é a terceira, tendo como finalidade principal colocar em relevo as originalidades de semelhante tumor.

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

ABSTRACT

In a meeting of the Pan-American Association of Ophthalmic Pathology, held in Los Angeles, CA, on October 10, 1991, at the Doheny Eye Institute, C.O. Degrazia proposed the name LOFONEUROGONIOMA for a single undifferentiated intraocular tumor originated in the cells of lamina fusca, with undifferentiated cells of expressive differentiation into Schwann cell, melanoblast and neuroendocrine cell lineages. In view of trimorphism, a pathologist may be led to a diagnosis of malignant melanoma, schwannoma or endocrine cell tumor. After this date, an article was published in Revista da AMRIGS, Porto Alegre, 52 (4): 261-272, oct-dec 2008, with collaboration of experts from the fields of Immunohistochemistry and electron microscopy. The current publication is the third one and its main purpose is to highlight the original characteristics of such a tumor.

KEYWORDS: *Lamina Fusca, Undifferentiated Tumor, Lofoneurogonioma, Neural Crest, Masson's Lofoneuroepithelium.*

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INTRODUCTION

The present work is the third publication on a tumor that affects a structure of the eyeball, the lamina fusca, a site where no pathology has been described and is very unlikely to give rise to a neoplasm. This publication is being brought to scientific literature again due to the desire to underscore the original aspects of the case. The list of original characteristics that I will make should be carefully accompanied with the figures, as they are the authentic documents on which readers should rely.

The case was first presented by me under the title of Choroidal Tumor, in the meeting of the Pan-American Association of Ophthalmic Pathology, held in Los Angeles, CA, on October 10, 1991, at the Doheny Eye Institute.

Having observed the progressive thickening of the lamina fusca (LF), in connection with the tumor, I showed images of its structure and proposed the name *Lofoneurogonioma* for the neoplasm. The word has a Greek origin, *lofos* = crest, *neuro* = nerve, *gonos* = origin, and *oma* = tumor, meaning: tumor of cells originated in the neural crest.

The second presentation was an article published in Revista da Associação Médica do Rio Grande do Sul (1), which includes the history, discussion, details related to the case, and names of the collaborators, both clinicians and experts in Immunohistochemistry, Pathology and Electron Microscopy.

The name *lamina fusca* originates from Latin, since *fuscus* means dark, due to the greater or lower amount of melanin present on its path, which may be evidenced by special stains, such as picrosirius, a dye that highlights collagen in intense red, as shown in figure 1.

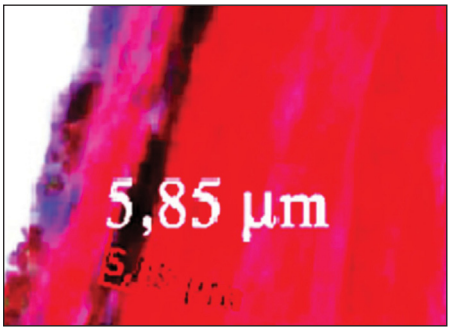


FIGURE 1 – Lamina fusca evidenced by picrosirius stain, measuring around 6 micra in thickness.

In view of its diminutive thickness, measuring around 6 or 7 micra, it can only be seen with a light microscope, with some difficulty though, as it is confused with the choroid, which encloses it on the inner side of the eye.

This difficulty is sometimes overcome because the paraffin impregnation techniques used for preparing histological sections separate it from the choroid and the sclera that encloses it externally, causing an artificial detachment. This is seen in figure 2.

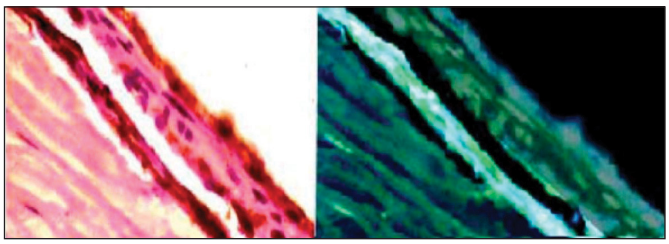


FIGURE 2 – artificial detachment of Lamina fusca. The LF is seen between the sclera and the uvea which maintains the retinal epithelium. The retina is not seen because it was also artificially detached, as shown in figure 4.

The figure 3, marked with letter C, viewed at low magnification, shows the beginning of the LF hyperplasia, located between the two arrows.

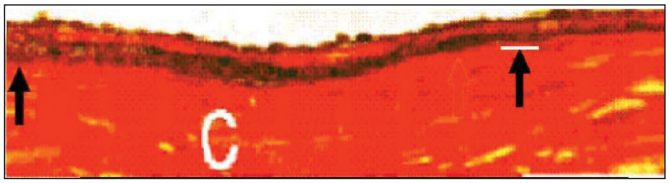


FIGURE 3 – The two arrows signal the beginning of hyperplasia. Picrosirius staining.

1st Original Aspect: Tumor Shape

Choroidal tumors that reach a certain size, from a few millimeters, show a convex inner surface. I have never seen, under these conditions, a melanoma with a different shape. They should not be mistaken with nevi, which may have a flat surface.

When they disrupt the Bruch's membrane, the mushroom-shaped ones always show a convex surface.

In the photograph of the specimen, figure 4, the white arrow points to the tumor concavity. The tumor mass is whitish and has a very wide base.

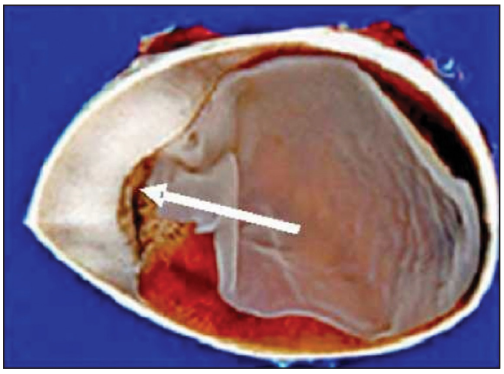


FIGURE 4 – Section of the specimen showing wide neoplasm with concave internal surface (marked by the arrow) with rugged aspect indicative of rupture of the Bruch's membrane, artificial detachment of retina, and uveal staining in the background.

On the fluorescein angiographic report, I highlight the following findings:

Scarcely pigmented tumor, rupture of the Bruch's membrane, intraretinal invasion, no nourishing vessels are seen. The conclusion is *amelanotic melanoma.*

The expression *with intraretinal invasion*, used on the report, should not be understood as having the same meaning as in pathological anatomy, in which the word *invasion* means the penetration of malignant cells into a tissue, the retina is never invaded by cells of a choroidal melanoma.

The findings mentioned are all supported by the histological study and may serve to differentiate it from choroidal melanoma.

The echography report is brief, showing a tumor with a wide base – confirmed by the anatomopathological study – and arriving at the conclusion that it is a choroidal melanoma. By observing the figure, an expert could describe other characteristics, such as the concave aspect and retinal detachment.

2nd Original Aspect: Nerve/Tumor Relationship.

The three photomicrographies of figure 5 were included to show the differences of LF with a nerve extending alongside. In the first image, the LF is observed to be already thickened, so it is easy to differentiate it from the smaller, light-colored Schwann cells of the nerve.

Malignant cells begin to invade the nerve, whose thickness increases, as seen in the middle picture, and its fibrils are completely dissociated, *as in an explosion* (right photo). The finding of nerve fillets sometimes completely isolated within the neoplasm is explained, as they are extensions from the same nerve. The stains employed were: *hematoxylin-eosin, S-100 Protein, and luxol,* respectively. The insert in the middle figure is the cross-section of an axon, showing the peripheral myelin, which is strongly responsive to S-100 Protein, and the central axis cylinder, aspects that have long been described in scientific literature, but have been seldom shown.

3rd Original Aspect: Measurements Of Lamina Fusca

The third original aspect lies exactly on the measurements of LF. These measurements do not appear in the literature on eyeball histology that is typically consulted.

The figures of PLANK 1, from **a** to **h**, show progressive thickening. In each of them there are numbers expressing thickness in micra. The thinnest measures 9.29 micra, increasing up to 103.25 micra. Measurements were taken with the LF at a slant position, therefore, they are slightly

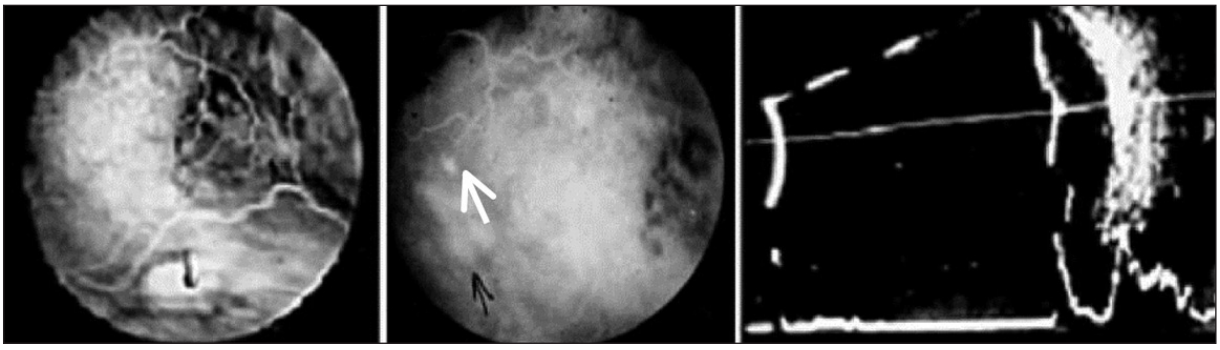


FIGURE 5 – Fluorescein angiography report: RE Fluirescein angiography study confirming the presen poorly pigmented tumor-like lesion which disrupted the Bruch s membrane, with intra location. It shows dye leaks (Arrow) and areas of fluorescein blockade, but nourishing vess not individualized possibly due to an intraocular tumor. The aspect is that of an ame melanoma with retinal invasion. The fluorescein angiography is not able to provide an a diagnosis. Echography report for the RE. Reveals the presence of a tumor mass with a large Echography study consistent with choroidal melanoma. Retinal service at Hospital Banco de de Porto Alegre.

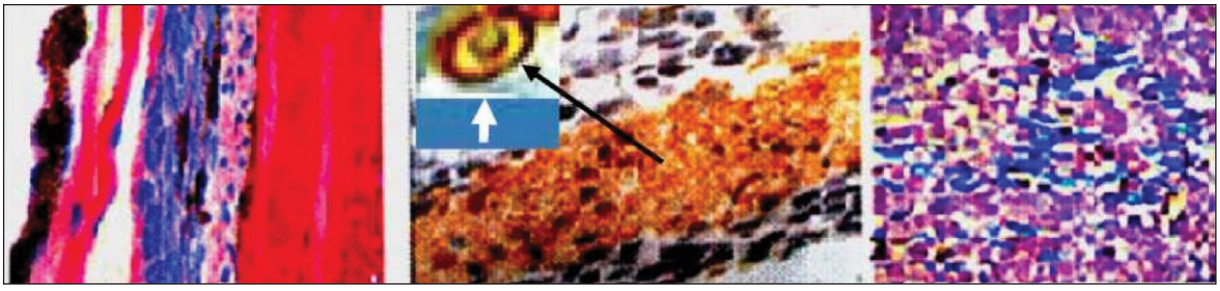


FIGURE 6 – Nerve-tumor relationship. In the left picture, the retinal epithelium, the uvea, the thickened lamina fusca, a lighter bundle of nerves and the red sclera are noted, At the center, the nerve, evidenced by the S-100 protein, is seen beginning to be invaded by malignant cells. In the inset, there is a highly magnified axon, with peripheral myelin and central axis cylinder, separated from the nerve on purpose. In the right picture, the luxol fast blue stain shows axons dissociated by tumor cell.

greater. The pigmented epithelium, with melanin grains, may serve as a comparison, as the cell thickness ranges from 6 to 20 micra. The retina cannot be seen because it was artificially detached. The following three pictures, **i, j, k,** are photos of the histological structure of the tumor. The left one, **i**, is the LF with an anarchical arrangement of its cells, where a vascular bed is invaded by malignant cells. The two following, **j** and **k**, show palisades having the same arrangement as that of the embryonic epiblast from which they derive. Figure **m** shows cells from a tumor surface smear stained by the Papanicolaou method, with nuclei having the shape of a cufflink. On both sides, two nuclei, figures **l** and **n**, viewed by an electron microscope, show deep clefts that account for the nucleus shapes seen under the light microscope.

4th Original Aspect: Neural Crest And Lofoneurogonia

Usually, neurulation is represented with cross-sections, but we should consider it all along the longitudinal length, from the cephalic region to the caudal region, the neural crest is, therefore, bilateral and rostrocaudal.

— Origin of LF cells in the neural crest

1º - Evidence from the tumor

The same figure 7 from the work mentioned in (1) shows the correlation between tumor cells and embryonic cells. (In this case, a rat embryo was used for comparison.)

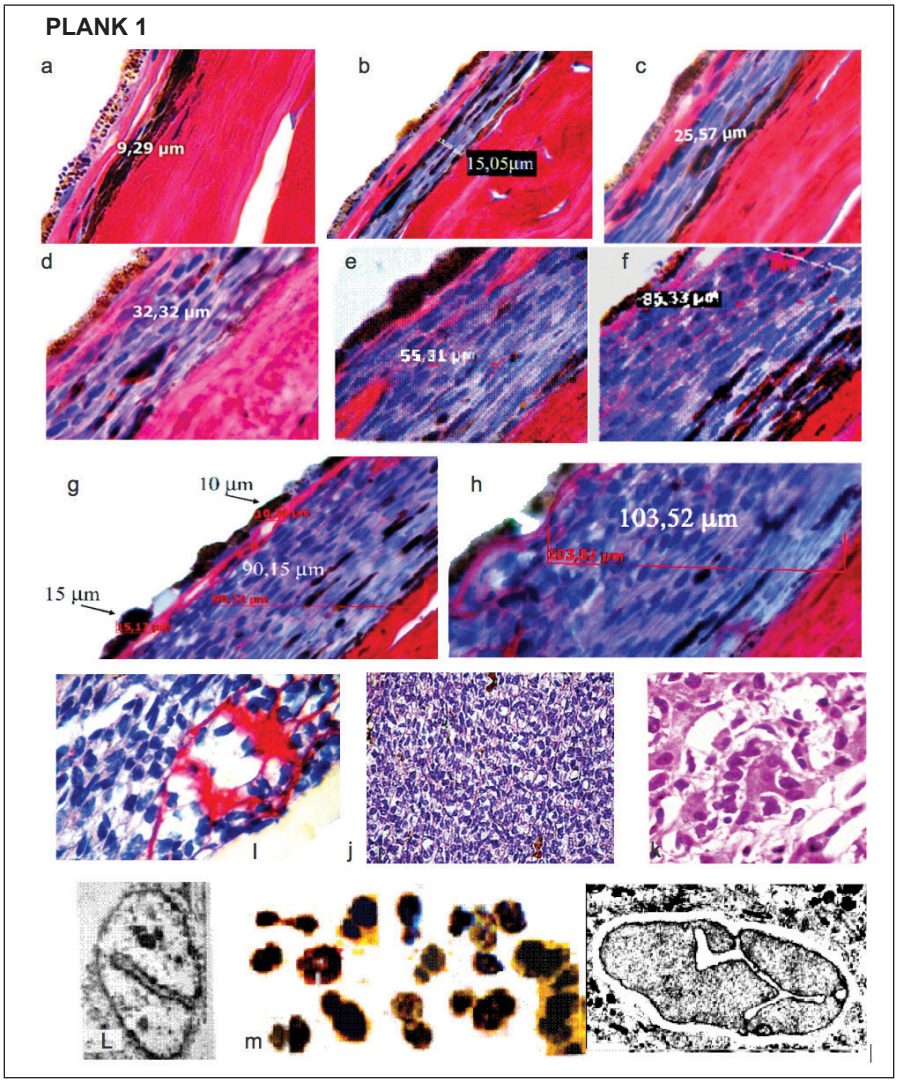


FIGURE 7 – PLANK 1 – Legend: LF sections are presented whose thickness gradually increases, as seen by the numbers accompanying each picture, until they turn into a malignant tumor. (The measurements were taken using an application, Axion Vision, Release 4,6,3, (04-2007) provided by the microscope supplier, Carl Zeiss do Brazil Ltda). In figure (g), cells of the pigmented epithelium were measured with the purpose of comparing them with those of LF. Figure (i) is gross evidence of the metastatic pathogenesis, as it shows malignant cells invading a vascular bed and entering the bloodstream. Figure (h) shows the formation of palisades at its beginning, these are seen in profusion in figure (j) of the tumor, taking on the shape of migrating birds in flight or of a paraglider. Figure (m) consists of cells from the direct smear of the neoplasm, stained by the Papanicolaou method and viewed using a light microscope with oil immersion (100 X magnification), showing a cufflink shape. In (l) and (n), at magnification of 16,000 X, nuclei are shown with grooves that account for the cufflink shape in light microscopy.

The cell palisades, which resemble migrating birds in flight, present evidence of being derived from the embryonic epiblast. Likewise, undifferentiated intermediate cells, which differentiate into Schwann cells, melanoblasts or endocrine cells, derive from the neural crest.

Despite the difficulty establishing these correlations, it is accepted that melanocytes derive from the neural crest. An elucidative approach is made by (2), from which I took the following excerpts

Currently, it is accepted that, cytogenetically, melanomas are of neuroectodermal origin, from melanocytes derived from the neural crest. This origin is supported by confirming the association of uveal melanomas with abnormalities in the nervous system, such as neurilemomas, (…).

Later it adds: *Furthermore, in some cases, there are light tumor areas similar to Schwann cells, adjacent to other areas of evident melanomatous appearance, highly pigmented.*

2º Evidence from experimentation

Some elegant evidence is reported in the same book as follows:

If the optic vesicles from a bird are transplanted to the coelom of another, before the cells from the neural crest migrate, only cells of the retinal epithelium are pigmented, but no choroidal melanoblasts appear, which indicates a different origin for both pigments.

If the transplantation is carried out after the emigration of cells from the neural crest, melanocytes appear in the uwea having characteristics of the donor.

These experiments are attributed to several authors, listed in the Bibliography on page 28 of the same book.

How the neural crest cell migrates, what its initial gene pool is, what influences affect the cell when it crosses different tissues, whether it is always migrating or remains dormant are compelling questions.

In figure 8 and PLANK 2, I try to provide a notion about the links derived from cells originated in the neural crest. A

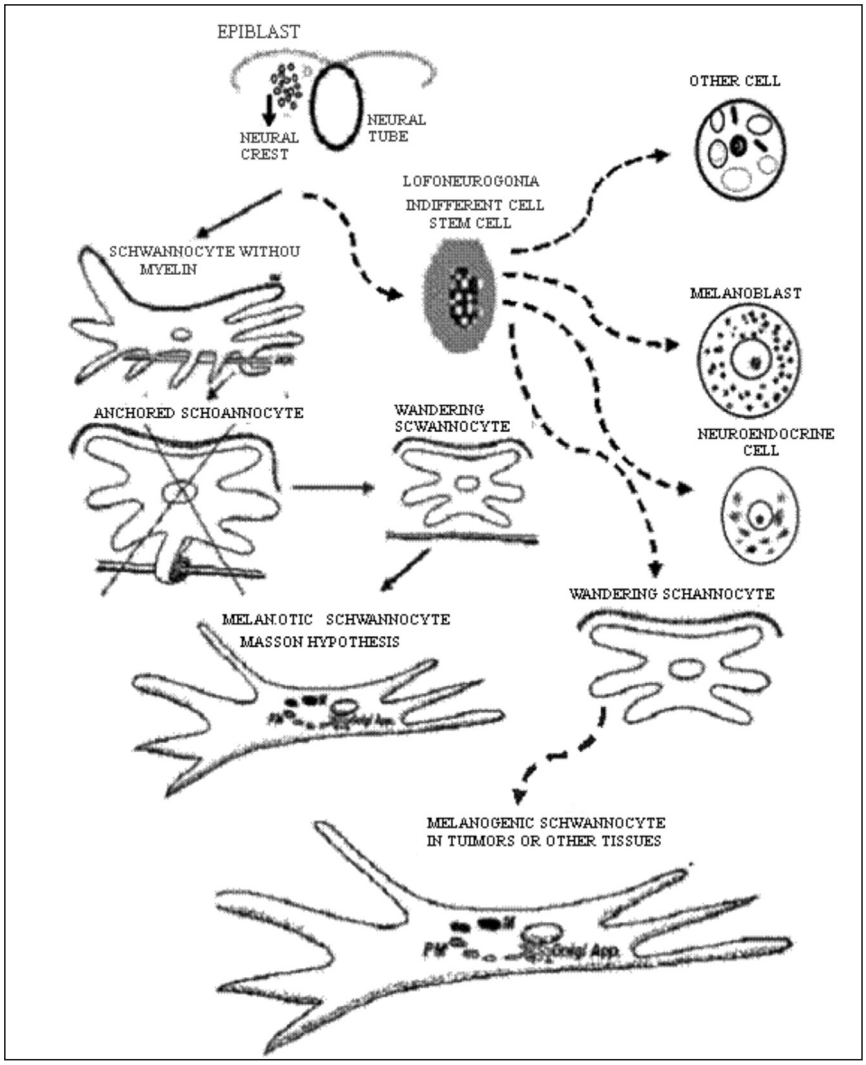


FIGURE 8 – From the NEURAL CREST, undifferentiated cells may follow two paths: On the left, indicated by straight arrows, representing classic theories, a Schwann cell is detached from the anchored cell and by axonalstimuli, and other stimuli, it nests on tissues or tumors, and in accordance with Masson's hypothesis, it produces melanosomas. On the right path, which represents my conception, indicated by dashed, curved arrows, an indifferentiated cell, or source cell, the lofoneurogonia, migrates to tissues where it will from several lineages of Schwann cells, melanoblasts and neuroendocrine cells and others with secretions that have not been determined yet.

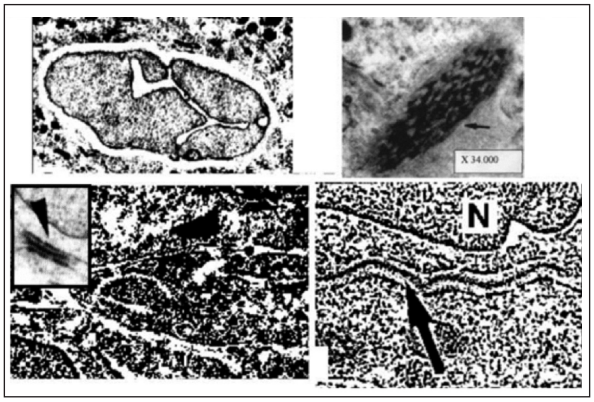


FIGURE 9 – Typical morphology of a Schwann cell: Lobulated nucleus with clefts, cytoplasm with numerous finger -like structures, incomplete basal membrane (indicated the arrow) and structure viewed at magnification of X34.G0G, comparable with the Luse Body, which was presented by the autor at magnification of X24,000. Letter N is indicating the nucleus. The arrow head in the insert indicates a cell junction.

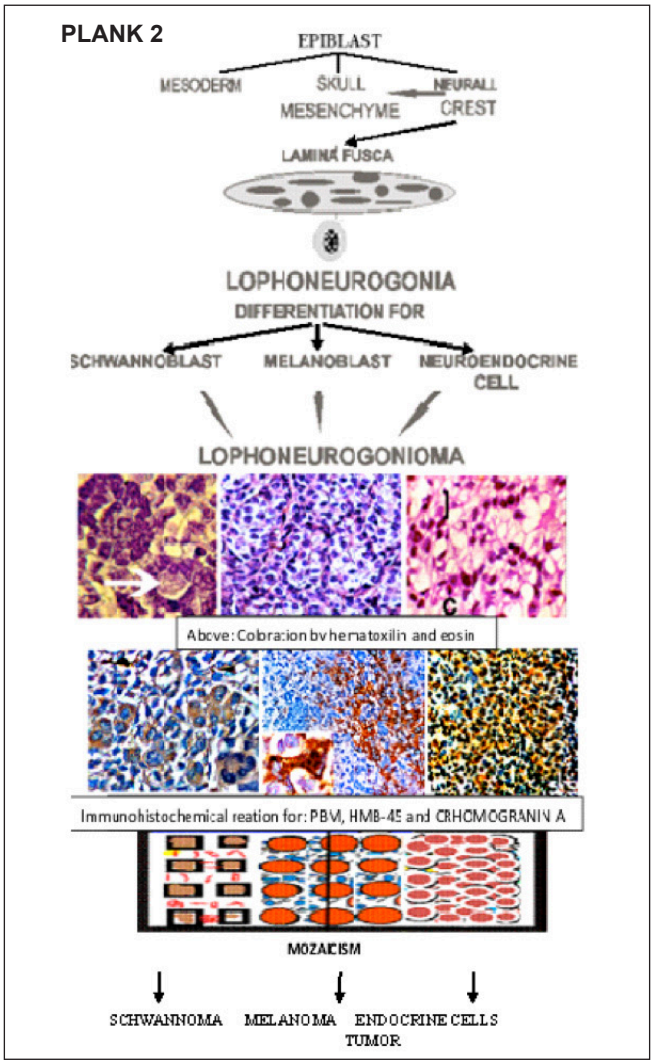


FIGURE 10 – PLANK 2 – Legend: In this plank, three main aspects of the work are included. 1. In the upper portion there is a scheme showing the derivation of neoplastic cells from an undifferentia ted cell of the neural crest, which I called lofoneurogonia. From it three arrows depart indicating the differential forms, schwann cells, melanoblasts and endocrine cells. These phenotypical forms were specifically characterized by specific immunohistochemical reactions, PBM, HMB-45, and CHROMOGRANIN A. The neural crest is a proliferation of the epiblast at a slanted angle for formation of the neural tube. II – I named the resulting neoplasm lofoneurogonioma. In the lower portion, the rectangle resembles a surface with three different ceramic plates, accounting for the word mosaicism for tumor trimorphism. III – Finally, trimorphism may lead to contradictory diagnoses of schwannoma, melanoma and endocrine cell tumor. In the insert with the melanoma picture, a strongly reactive melanoblast is highlighted.

historic study is found in (2) and (3), in which we see that since Masson and Berger (1923), who described a case of uveal ganglioneuroma with melanoblasts, schwann cells and other structures of nervous origin, the origin of some tumors in the neural crest has been accepted, and Masson raised the hypothesis that the Schwann cell is a facultative melanocyte, and Bollande (4) coined the word *neurocristopathy* for such neoplasms. Arising from the neural crest, a source cell, the *lofoneurogonia*, while migrating through the body tissues, is subject to two chief influences: The genes it carries and the chemical substances it encounters along its path – which by their turn are subject to a genetic chain – in the case of the skin and eyeball, the physical influence of light is added. If the environment is rich in tyrosine, a chemical cascade is formed from indol leading to the formation of melanin.

Among the theories on the genetic mechanism mentioned by (3), I prefer the third theory, according to which the migrating cell, known as source cell, has *equipotentiality*, with *environmental specification*.

Based on what was described, the disagreements between pathologists to which the same tumor is submitted can be understood.

It is curious and important to show the data on which specialists relied to provide different diagnoses:

1st - Diagnosis of Schwannoma

A – Electron microscopy:

B – Immunohistochemistry:

PLANK 2 shows how an undifferentiated tumor may present multiple cells, which, despite having the same origin and being present in the same tumor, are phenotypically different. Metastases can show the same multiplicity, neoplasia being, therefore, a real mosaic. The word mosaicism is used in genetics to characterize the difference in the number of chromosomes, as in Trisonomy 21, or Down Syndrome. I make use of the same word to refer to neoplasms with some degree of undifferentiation, and with phenotypically different cell lineages. These are tumors with a mosaic-like structure which, according to the technique used by the investigator, show different aspects under different nomenclature, accounting for the substantial diagnostic disagreement.

CONCLUSION

In this paper, I intended to present the several original aspects shown by a tumor that has not been described in scientific literature before. It should be noted that its origin is in the lamina fusca, a site in which no anatomopathological process has been described. In the photomicrographs, the progressive thickening of LF is curious and evident, and so is the appearance of palisade cells and the invasion of vascular beds at the end of the thickening, near the neoplasm, which is formed by undifferentiated cells with three phenotypical lineages, Schwann cells, melanoblasts and neuroendocrine cells, all derived from a source cell originated in the neural crest, called *lofoneurogonia* by me. Hence the designation *lofoneurogonioma* that I assigned to the tumor. The resulting trimorphism, which I call mosaicism – actually, more than three forms are assumed to exist – accounts for the diverging diagnoses among pathologists.

The individuality of LF is documented in figures 1 and 2, which is not found in publications addressing this structure.

The artistic quality of the work stands on its own.

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1 - Ocular Pathology Laboratory (Private Institution).

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4 - Retinal Center, Banco de Olhos Hospital, Porto Alegre, Rio Grande do Sul: complementary tests (echography, retinography).

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