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CLINICAL AND ELECTRON MICROSCOPIC FEATURES OF RETINOBLASTOMA

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INDEXING WORDS

histopathology; transmission electron microscopy; retinoblastoma

SYNOPSIS

A male child of 1-year, 6-month-old had a history of leukocoria of the left eye for approximately three months prior to admission into our facility. No abnormality was found in the right eye. There was negative family history of retinoblastoma. Ophthalmoscopy revealed a white mass extending from the supero-posterior part of the left globe to the posterior surface of the lens. Orbital tomograms showed no intraocular tissue densities in the mass but a B-scan ultrasound showed an echo dense area of the mass. Histopathologically areas of

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photoreceptor differentiation and Flexner-Wintersteiner rosettes were observed in the tumor mass by light microscope. Transmission electron microscopy disclosed the presence of prominent mitochondria on the luminal side of the cells forming rosettes and these were believed to be the component parts of the inner-segments of the photoreceptor cells.

The results of this study indicate a predominant neuronal nature of the neoplastic cells with photoreceptor-like differentiation.

INTRODUCTION

Retinoblastoma is the most common intraocular tumor of infancy and is world-wide in distribution affecting all racial groups without sex predilection. The genetic cause of retinoblastoma was found to be the loss of both alleles of a normal tumor suppressor gene(the RB gene) on the long arm of chromosome13.[1] Investigators have shown that mutations of the RB gene also play a role in the development of a large variety of malignant tumors.[2,5]

On histological examination, retinoblastoma shows different degrees of anaplasia and differentiation.[6,8] It is generally agreed that the photoreceptor cells of the retina are members of neuronal cells. Some investigaors believe that the tumor cells in retinoblastoma may differentiate into photoreceptor-like cells or elements. Many years ago Rudolph Virchow[9] considered a glial cell origin of the tumor and so, he named the tumor as "glioma". On the other hand, a different groups of researchers at a latter period suggested the nuronal origin of the tumor specially on the basis of the ultrastructural and immunocytochemical examinations.[4,7,10] Despite numerous investigations, the histogenesis of this tumor is still disputed. We herein present a case of retinoblastoma describing its clinical, histopathologic and electron microscopic features.

ABRIDGED CLINICAL INFORMATIONS

General examination

A male child of 1-year, 6-month-old was consulted for the complaint of a whitish mass in the left eye for approximately 3 months. There was no history of weight loss or systemic diseases. Family history was negative for any major eye diseases, retinoblastoma or other neoplasms. There was no history of hypertension or diabetes mellitus in the family.

Ophthalmic examination

Ocular examination showed visual acuity 0.1 in the right eye(by Preferential Looking Method) and only perception of finger movement in the left eye without correction. Extraocular muscles were full and orthophoric. Eyelids, eyelashes, conjunctiva, cornea and sclera were found to be normal in each eye. The anterior chamber was clear in both eyes. There was no lental opacity in either eye. A large white mass was seen to extend from the supero-posterior part of the left globe to the posterior surface of the lens. Pupillary reflexes were normal in both eyes.

Laboratory examination

Blood examinations including cell count and electrolyte values were normal as were urinalysis and liver function tests. Immunological tests were negative for carcinoembryonic antigen and α-feto-protein. Diagnostic B-scan showed an echodense area of the mass. Orbital CT and MRI revealed no abnormality. The patient underwent a surgical enucleation of the left eye with implantation of an artificial eye.

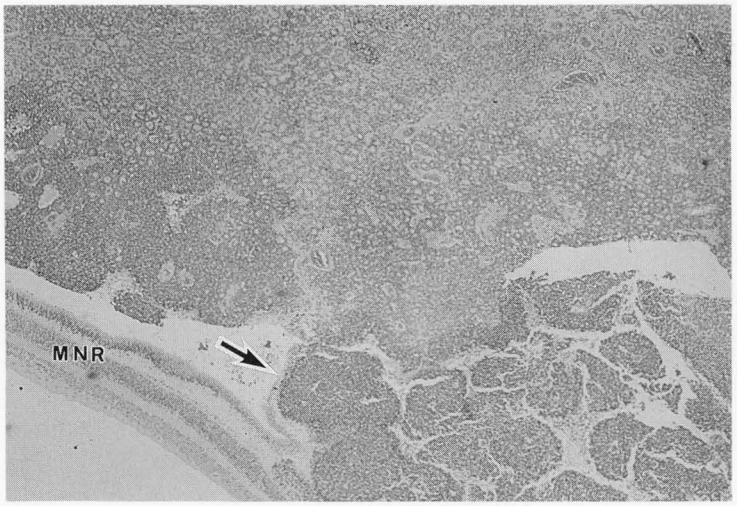

Fig.1.

Endophytic retinoblastoma is seen in the photomicrograph(arrow).

MNR- morphologically normal retina. (H.E., x100)

METHODS

Formalin-fixed and paraffin-embedded retinoblastoma specimen was used in this study. Paraffin block was sectioned at 5μm thick and stained with hematoxylin and eosin for histologic observations. For transmission electron microscopy, formalin-fixed tissue was also used. Portions of the tumor tissue were fixed in 2.5% buffered glutaraldehyde and embedded in Epon. Sections of 60-70 nm thickness were prepared using a "REICHERT ULTRACUT S" ultramicrotome and observed with a Hitachi H-600A electron microscope.

RESULTS

Gross pathology

The eyeball was 20x20x17 mm in size. A 6 mm segment of the optic nerve was attached to the eye. The cornea measured 11x10 mm. The eyeball did not transmit light. The globe was opened in the horizontal plane. No abnormality was seen in the anterior chamber. The lens was in place. The ciliary body was not swollen. The vitreous was liquid and the cavity was reduced because of the tumor mass. The retina was infiltrated by the tumor cells. The tumor was 15x8x8 mm in size. The sclera was unremarkable.

Microscopic examination

Microscopic examination revealed no abnormality in the cornea, anterior chamber, trabecular meshwork, iris, lens and the ciliary body. The tumor displayed an endophytic appearence(Fig.1). Several areas of photoreceptor differentiation were easily identified under low power magnification. They were seen as pale eosinophilic areas, clearly recognizable from the basophilic masses of

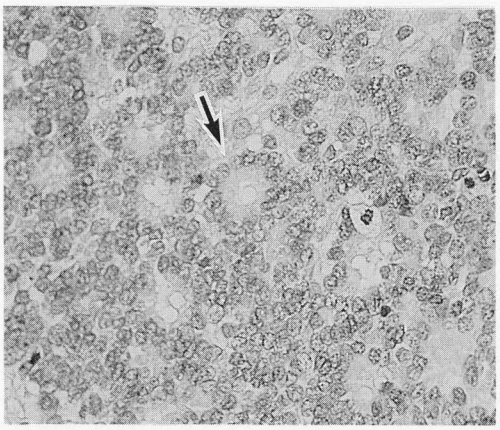

Fig.2.

Well-differentiated area of the neoplasm containing Flexner-Wintersteiner rosettes(arrow). (H.E., x400)

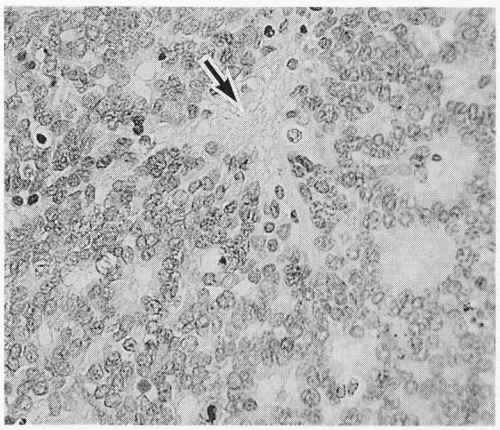

Fig.3.

Photomicrograph of the tumor shows areas containing glia(arrow) and Flexner-Wintersteiner rosettes. (H.E., x400)

undifferentiated tumor cells. Undifferentiated retinoblastoma cells constituted the main bulk of the tumor and mitotic figures were frequently observed in these cells. There were areas of Flexner-Wintersteiner rosettes(Fig.2,3). Small areas containing glia(Fig.3) and necrosis were occassionally noted in the tumor. With these findings a diagnosis of moderately differentiated retinoblastoma was made.

Electron microscopy

The retinoblastoma cells that were differentiated into photoreceptor-like cells, formed long processes containing prominent mitochondria. The differentiations were observed on the luminal side of the cells forming Flexner-Wintersteiner rosettes(Figs. 4,5). Majority of the other neoplastic cells displayed an undifferentiated appearence with large hyperchromatic nuclei and scant cytoplasm containing mitochondria and ribosomes. Occassional mitotic figures were clearly seen in the undifferentiated neoplastic cells.

DISCUSSION

The clinical manifestations of retinoblastoma vary with the stage of the disease. In the past, the more advanced stage of retinoblastoma with extraocular extension was the rule and treatment was mainly palliative. Common presenting clinical features included a fungating mass prolapsed through a perforated cornea, proptosis caused by massive orbital invasion, advanced secondary glaucoma and enlarged preauricular or submandibular lymph nodes due to metastasis. With the improvements of primary medical education and increased availability of eye care facilities, advanced cases are rarely seen now-a-days. Leukocoria is the initial manifestation in 60% of the cases in Japan.[3] In our study the patient presented

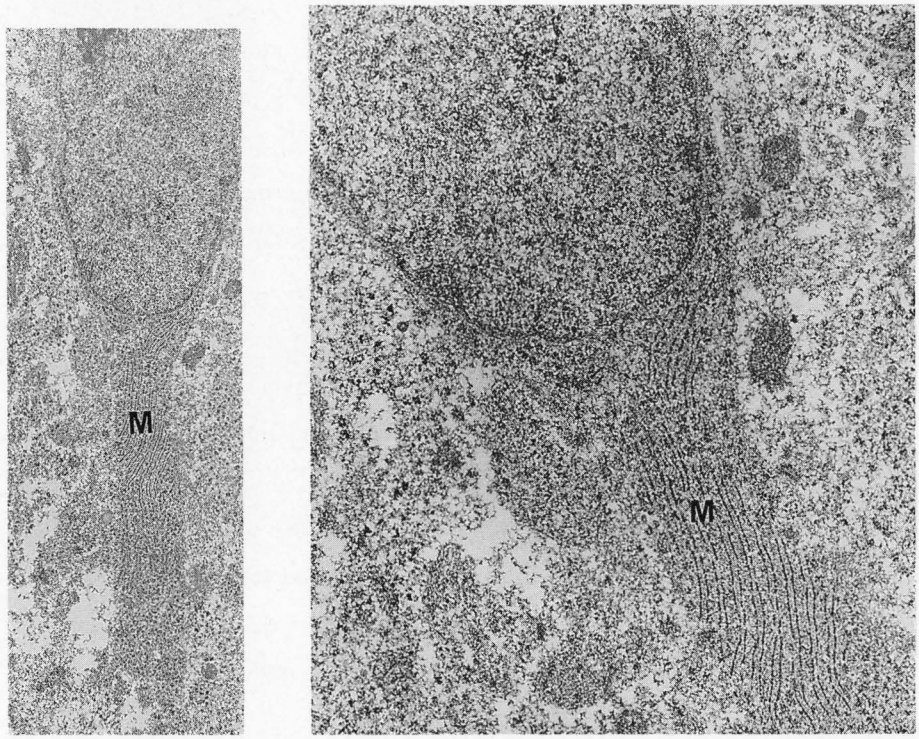

Fig.4.

Electron micrograph of photoreceptor cell elements in retinoblastoma. The cell process extends beyond the plane of the cell attachment for a variable distance. Longitudinally oriented mitochondria(M) in large numbers are packed in the cytoplasmic process. (x9500)

Fig.5.

Mitochondri(M) in the cell process of photoreceptor-like cells of retinoblastoma viewed under higher magnification. (x24000)

with a leukocoria with relatively slow progression. There was no family history or hereditary pattern. So we concluded that our case was sporadic in incidence.

It is apparent from the histologic appearence described above that photoreceptor differentiation of retinoblastoma can be easily distinguished from undifferentiated tumor cells. It may be noted here that massive gliosis of the retina can also be recognized from the above areas. Histologically, the proliferating astrocytes in massive gliosis are larger in size and spindle-shaped, containing large oval nuclei. The demonstration of areas of photoreceptor differentiated or undifferentiated tumor cells with the presence of Flexner-Wintersteiner rosettes establishes the diagnosis of retinoblastoma.

In previous electron microscopic studies the photoreceptor differentiation in retinoblastoma has been recorded.[7,8] In our study we observed that the luminal side cells of the rosette had long processes containing prominent mitochondria. Inner segment of the photoreceptor cell in the normal retina has similar structure. So we can say that these cells were differentiated into photoreceptor-like cells.

The findings of this study suggest that the retinoblastoma in our patient is predominantly a neuronal tumor with significant photoreceptor differentiation.

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