THE VALUE OF ESTIMATION OF TUMOR MARKER IN RETINOBLASTOMA

Thesis

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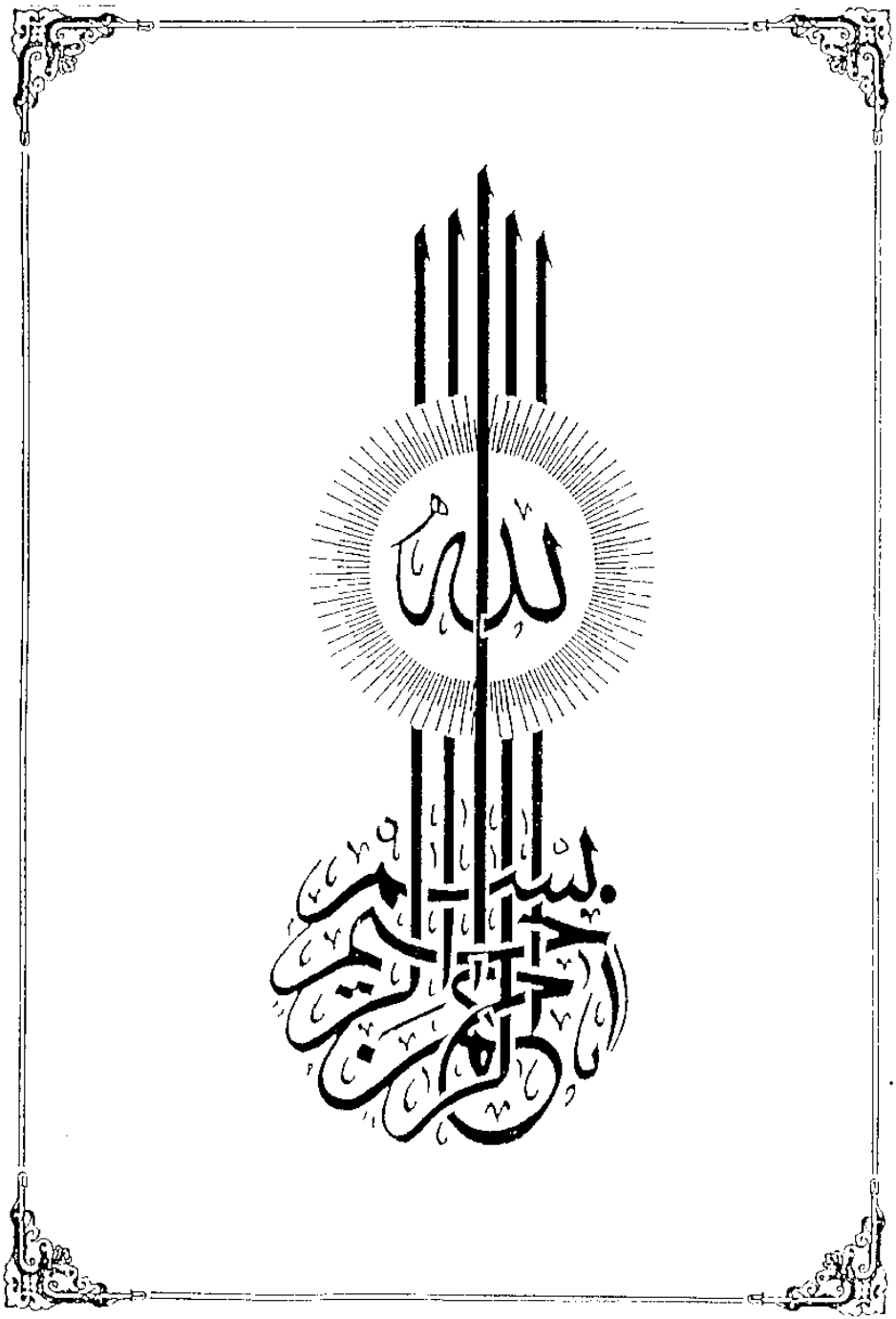

CONTENTS

INTRODUCTION

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Retinoblastoma is a malignant tumor which affects children and may cause unilateral or bilateral blindness or even an agonizing death (Elmassri, 1981). It is the most common intraocular malignancy of childhood (Haik et al., 1985) and is one of the most frequent of all childhood malignancies being responsible for approximately 1% of all deaths from cancer in the age group under 15 years (Puklin, 1980).

During the last 14 years, after the establishment of the Retinoblastoma unit in Ain-Shams University, many frequent cases are referred from all other ophthalmic centers all over Egypt and nearby countries. These cases made a good material so that a series of thesis had been undertaken dealing with different aspects of the retinoblastoma. In continuation of this series, study of tumor markers in cases of retinoblastoma is the subject of this thesis. These are substances that are produced by cancer cells and appear in the circulation of cancer patients at a higher concentration than in individuals without cancer (Lakish, 1978). Of these, we studied two markers which are Alphafetoprotein (AFP) and Carcinoembryonic antigen (CEA) for purposes of early diagnosis, follow up and detection of cases liable to have the condition.

REVIEW OF LITERATURE

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Retinoblastoma

Historical Aspects and Nomenclature:

Petrus Pawius of Leiden (1597) was probably the first to describe the entity we now recognize as retinoblastoma. In 1767, a very accurate description of bilateral retinoblastoma was given by Hayes London (Dunphy, 1964). James Wadrop of Edinburgh was credited as the one who in 1809 established retinoblastoma as an entity and was the first to advocate early enucleation as a life saving measure (Duke Elder, 1967).

Scarpa (1816) stated that complete extirpation of the eye is useless and rather accelerate the death of the patient. Guthric (1823) described a lesion which he called (Fungus Haematoides) as a fatal disease to which removal of the eye has not succeeded in arresting its progress when it has been fully formed in the bottom of the eye. With the advent of microscope and the ophthalmoscope and introduction of chloroform anesthesia Virchow (1864) correctly identified retinoblastoma as a neoplasm which he called glioma of the retina in the belief that the tumor arose from glial cells (Reese, 1976).

In 1891, Flexner and in 1897, Winterstiener described the rosettes that are frequently found in the tumor. They believed that the tumor arose from precursor cells of the neuroepithelium i.e. photoreceptors and called it a neuroepithelioma (Yanoff and Fine, 1982). Verhoeff of

Boston convinced the American Ophthalmological Society in 1926 to adopt the term retinoblastoma which he had suggested in 1922. Verhoeff recognizing that the tumor was basically an undifferentiated neuroblastic neoplasm derived from hypothetic retinoblasts joined the logical name, which has gradually replaced virtually all others that have been proposed from time to time (Verhoeff and Jackson, 1926).

Parkhill and Benedict (1941) also proposed different names to reflect varying degrees of differentiation, retinoblastoma for undifferentiated tumors and neuroepithelioma for tumor containing rosettes. Tso, Fine and Zimmerman (1969&1970) demonstrated the presence of photoreceptor differentiation (fleurettes) in retinoblastoma.

According to Offret et al.(1974), the term retinocytoma has been used in the French literature to designate the most highly differentiated form of retinoblastoma. They divided retinocytomas into two groups: one characterized by large number of highly differentiated Flexner-Wintersteiner rosettes; the other by fleurettes.

Gallie et al.(1982) introduced the term "retinoma" to describe a group of small often partially calcified but viable, retinal tumors which showed no tendency to grow over long periods of follow up. However, non of these tumors was examined histologically and they probably represent examples of spontaneous regression (Elmassri, 1988).

Margo, et al. (1983) described the histopathology of a group of retinal tumors treated primarily by enucleation that differed from typical

retinoblastoma in showing non of the histopathologic features or intraocular growth characteristics of malignant neoplasms. They believed that these tumors were identical with the (retinomas) described by Gallie and co-workers (1982). However, they considered the term retinoma as a non-specific one because it can be applied to any retinal tumor whatever its origin. Hence, they re-introduced the term retinocytoma and restricted its use to tumors in which adequate histological sampling reveals benign tendency.

Incidence and Epidemiology:

Incidence:

Retinoblastoma is world-wide distribution, its incidence is estimated to range from 1:35,000 to 1:15,000 live births and is expected to double over the next 100 years partly due to increased level of enviromental pollution (e.g., by military and civil radiation sources) and partly due to increased survival rates of retinoblastoma receiving adequate treatment patients with subsequent transmission of the disease to their offspring (Ellsworth, 1985).

Race:

It is world-wide in distribution affecting all racial groups, with a higher incidence in some black population as in Haiti, Jamaica and Nigeria (Sang and Albert, 1982).

Age:

The average age of incidence is thirteen months with 89% diagnosed before 3 years of age. It is rare after 7 years (Yanoff and Fine, 1982). It has been observed in premature babies (Zimmerman, 1985) and in patients as old as 52 years (Makley, 1963).

Sex:

There is no significant sex prevalence for occurrence of retinoblastoma (Yanoff and Fine, 1982).

Bilaterality:

In bilateral cases the retinoblastoma originates from separate sites in the two eyes; it is extremely rare for the disease to extend from one eye to the other via the optic nerve (Reese, 1976). Bilaterality occurs in 20-35% of all cases (Yanoff and Fine, 1982).

Genetic Aspects and Onchogenesis:

Retinoblastoma cases are classified according to the presence or absence of a family history into familial (6-10% of cases), and sporadic. About 25% of sporadic cases are heritable (Yanoff and Fine, 1982 and Zimmerman, 1985).

Therefore, retinoblastoma is better classified by Brude (1984) into:

1. **Non-heritable form:**

In which there is no family history of retinoblastoma, chromosomal

studies reveal no abnormalities and survivors do not pass the disease to their offspring.

2. Chromosomal deletion form:

It was found that 5% of retinoblastoma patients have a deletion of a part of long arm of chromosome 13 called 13 q 14 (Vogel, 1979). These children may have in addition various somatic and mental abnormalities (Matsunaga, 1980).

3. Heritable form:

This group includes all familial cases and 25% of sporadic cases. It is suggested that there is inherited mutation which renders all retinal cells as well as other somatic cells more susceptible to onchogenesis, so they differ from non-heritable cases in having: earlier age of onset tendency to bilaterality and multicentricity and susceptibility of the survivors to the development of other non-ocular cancers (Schipper, 1980 and Abramson et al., 1980).

In affected families, retinoblastoma is passed on as a Mendelian dominant trait with incomplete penetrance (80%) and variable expressivity. This means that at least one tumor in one eye will develop in 80% of genotypically affected persons and the variable expressivity includes total sparing of both retinae, total sparing of one retina, or sparing of variable portions of the retina in eyes with bilateral multicentric tumors (Zimmerman, 1985).

Origin of Retinoblastoma:

Since the retina and C.N.S. are formed from the same type of cells, they could be expected to have the same tumors. In fact, the primitive medullary epithelium of the neural tube lines both the primitive cerebral vesicle and optic cup. This primitive medullary epithelium can develop into either nerve tissue or supporting tissue. Thus tumors of the retina and central nervous system may be composed of very malignant undifferentiated cells (medulloblastoma and retinoblastoma) or benign differentiated cells (glioma and neurocytoma) or intermediate stage of differentiation (medullo epithelioma and neuroepithelioma i.e. differentiated retinoblastoma) (Zimmerman, 1985).

Pathology:

Retinoblastoma is essentially undifferentiated malignant neuroblastic tumor that may arise in any of nucleated nerve fiber or ganglion cell layers of the retina (Nicholson and Norton, 1980). Retinoblastoma has four presentations:

1. Exophytic Retinoblastoma:

When arising from the external nuclear layers, it tends to grow in the sub retinal space, pushing the retina inward and in late cases may gain access to the vitreous cavity. On ophthalmoscopic examination, one can see the retinal vessels coursing over the tumor. As the tumor grows larger, it may give rise to a total retinal detachment and tumor cells may

escape into subretinal exudate. Secondary implants may then develop on the outer retinal surface or on to the inner surface of retinal pigment epithelium and Bruch's membrane and pass into the choroid. From the choroid, tumor cells may escape along ciliary vesseles and nerves into the orbit or they may invade blood vesseles and become disseminated hematologically (Zimmerman, 1985).

2. Endophytic Retinoblastoma:

It grows mainly from the inner layers of the retina into the vitreous. Thus on ophthalmoscopic examination, one views the tumor directly. Retinal vesseles are typically lost from view as they enter the tumor. As endophytic tumors grow large and become friable, tumor cells tend to be shed from the tumor into the vitreous where they grow into separate tiny spheroidal masses that may be confused clinically with the (fluff balls) or (cotton balls) of inflammatory conditions as mycotic endophthalmitis.

Tumor cells in the vitreous also may become secondarily deposited onto the inner surface of the retina, where they may give rise to clinical difficulty in differentiation from independent new foci. Tumor cells in the vitreous also may spread into the posterior chamber and become disseminated by aqueous flow.

Secondary deposits or seeds on the lens, zonular fibers, ciliary epithelium, iris and trabecular meshwork may be observed, and tumor cells may follow the aqueous outflow pathways out of the eye. In such cases, the anterior segment changes may be misinterpreted clinically as

those of granulomatous iridiocyclitis (Zimmerman, 1985).

3. Mixed Endophytic-Exophytic Tumors:

They are probably more common than other purely exophytic or endophytic types, specially among large tumors. The combined features of both groups described above characterize these tumors (Zimmerman, 1985).

4. Diffuse Infiltrating Retinoblastoma:

They are the least common and often give rise to the greatest difficulty in clinical diagnosis (Nicholson and Norton, 1980). These tumors grow diffusely within the retina without greatly thickening it and may, therefore, escape clinical recognition. They also may be overlooked on ophthalmoscopic examination (Morgan, 1971). It is suspected by slightly older child, tends to be bilateral, presents with picture like granulomatous uveitis and can be diagnosed by ultrasound (Nicholson and Norton, 1980).

Microscopic Picture:

Retinoblastoma is composed of radiosensitive undifferentiated cells which appear small, round or polygonal, with scanty or almost invisible cytoplasm that stains poorly and a relatively large basophilic nucleus with numerous mitotic figures. The stroma is scanty and the tumor cells show little cohesion (Reese, 1976 and Zimmerman, 1985).

Rosette formation by tumor cells is highly characteristic of retino-