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Malignant Ocular Medullœpithelioma Diagnosed in an Adolescent Female at a Tertiary Health Facility in Southwestern Nigeria: A Case Report and Review of the Literature

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Abstract

Introduction: Intraocular medulloepithelioma is a rare, nonhereditary neoplasm of childhood arising from primitive medullary epithelium, often involving the ciliary body. It is a slow-growing tumour and most patients present between 2 and 10 years of age with loss of vision, pain, leukocoria and/or conjunctival congestion. It is difficult to estimate the true incidence of this tumour because of its rarity and paucity of large-scale population-based studies. To the best of our knowledge, this is the first reported case of histologically diagnosed primary malignant ocular medulloepithelioma in Nigeria.

Case presentation: We report the case of a 16-year-old female who presented with painful progressive left ocular swelling and visual deterioration of 8 years duration with associated redness and tearing. At presentation, a soft fleshy mass was seen protruding from the inferior aspect of the left eyeball, and enucleation of ocular contents was subsequently performed. Microscopic evaluation of the lesion showed distorted eye tissue with infiltration of the cornea, uveal tract and retina by malignant primitive neuroepithelial cells disposed in sheets, anastomosing cords and multiple classic Homer Wright rosettes with areas showing neuronal differentiation and marked nuclear atypia. The tumour also had a high mitotic index. The features seen were consistent with the diagnosis of a malignant teratoid medulloepithelioma. The patient had chemotherapy and radiotherapy and was subsequently discharged home for follow-up at the outpatient clinic.

Conclusion: Primary intraocular medulloepithelioma is a rare neoplasm occurring usually in the first decade of life. Before this, no case has been reported from Nigeria, especially in an adolescent female. The mainstay of treatment is surgery with chemo-radiation. This case also highlights the challenges involved in arriving at a definitive diagnosis.

Keywords: ciliary body; malignant medulloepithelioma

Introduction

Intraocular medulloepithelioma is a congenital but non-hereditary tumour of the non-pigmented ciliary epithelium and it is the second most common primary intraocular neoplasm seen during the first decade of life [1]. Histologically, the tumour resembles the medullary epithelium of the embryonic neural tube and the developing neurosensory retina [1]. Intraocular medulloepithelioma is a slow growing tumour with a better prognosis than medulloepithelioma of the central nervous system, despite having some similar morphologic features [1]. Confusing names attached to intraocular medulloepithelioma in the past have hampered effective communication and probably delayed a logical system of classification for tumours of the ciliary epithelium. Frederick Verhoeff described medulloepithelioma in 1904 as terato-neuroma, probably due to the heteroplastic tissue that he observed within the tumour [2]. Several years later, the Viennese ophthalmologist Ernst Fuchs introduced the term diktyoma (from diktyon: Greek word for net) because the microscopic appearance of interlacing bands of neuroepithelial cells was netlike [3]. Grinker [4], in 1931, borrowed the term medulloepithelioma from the seminal work on the related brain tumour by Bailey and Cushing. In the 1970s, Lorenz Zimmerman [5, 6] proposed a system for classifying primary tumours of the ciliary epithelium, as well as the conceptual framework for understanding the cellular polymorphism of medulloepithelioma. The World Health Organization adopted this nomenclature in 1980 and it has been in use since then [7].

This aim of this case report is to highlight the rarity of the tumour and the challenges that can be encountered before making a definitive diagnosis.

Case Presentation

Here we present the case of a 16-year-old Nigerian female who developed a severe reduction in vision in her left eye with associated gradual protrusion of the eyeball, redness and tearing. Visual acuity progressively deteriorated over 8 years until there was a total loss of vision in the eye. She had presented earlier in some hospitals where total enucleation of the left eyeball was proposed. However, the patient had always declined to give consent for surgery. On examination and work-up at the University College Hospital, Ibadan a soft fleshy tissue was seen protruding from the inferior aspect of the eyeball. After adequate counselling, the patient gave consent for a partial enucleation of the lesion.

Microscopic evaluation of the lesion showed distorted eye tissue with infiltration by neuroepithelial cells disposed in trabeculae, cords, pseudo-glandular patterns and rosettes (Figure 1). In some areas, the tumour cells showed marked pleomorphism with large vesicular nuclei, prominent nucleoli and disposition in sheets. Multiple atypical mitotic figures were also noted. The peri-tumoral stroma was predominantly acellular and myxoid with areas showing brain-like differentiation (Figure 2). These histo-morphologic features are consistent with the diagnosis of a malignant teratoid medulloepithelioma.

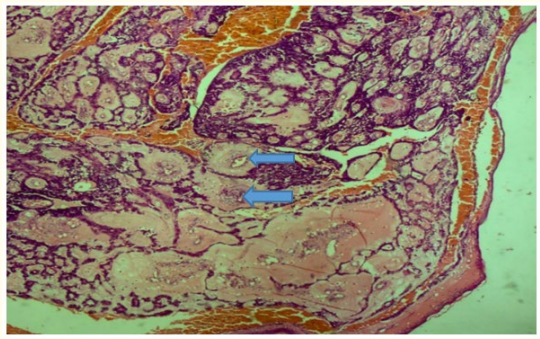

Figure 1: Photomicrograph showing malignant round blue cells disposed in tubules, trabeculae and Homer-Wight rosettes (blue arrows). Haematoxylin and eosin stains (X40 magnification).

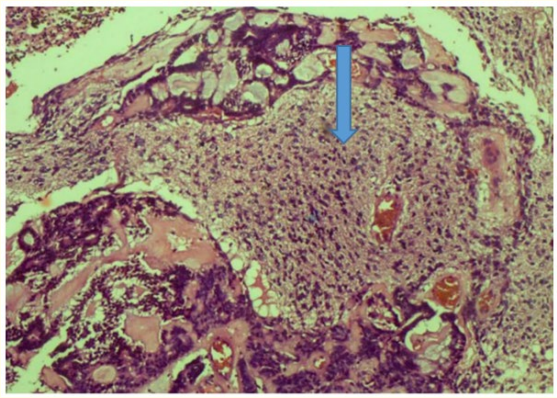

Figure 2: Photomicrograph of tumour showing the peri-tumoral stroma with areas of brain-like differentiation (blue arrow).

The patient also had chemotherapy and radiotherapy and was subsequently discharged home for follow-up at the outpatient clinic. The patent has been clinically stable with no complications or remission up to the time of writing this case report.

Discussion

Intraocular medulloepithelioma is a nonhereditary neoplasm of childhood arising from primitive medullary epithelium [8] and affecting the non-pigmented ciliary epithelium [2, 6], often involving the ciliary body [8]. The human retina is derived from the optic cup, which is an outgrowth of the medullary epithelium of the medullary tube [8]. Medulloepithelioma has an appearance similar to this primitive retina and medullary epithelium of brain tissue seen before 6 weeks of gestation [8].

There is a dearth of population-based information on the incidence and prevalence of medulloepithelioma, the literature consists largely of single case reports and small case series [9-12]. The largest case series was reported through the Armed Forces Institute of Pathology (AFIP), it involved 56 histologically confirmed cases with age range of 6 months to 41 years and mean age of 3.8 years at clinical presentation [9].

Medulloepithelioma is most often detected in children and rarely in adults with the age of presentation typically between 2 and 10 years [9, 12, 20, 21]. About 75-90% of the tumours manifest in the first decade of life [20]. However, there are well-documented cases of medulloepithelioma occurring in aduldhood [22-25]. The age of presentation has been known to vary between 6 months and 79 years [9, 12, 22-24]. There appears to be no gender or racial predilection [9, 12, 20, 21]. It is typically unilateral, with no preference for either eye [9, 12, 20, 21].

Due to their insidious onset and relative rarity, medulloepithelioma cases are often managed inappropriately for months or years before the correct diagnosis is established. This is highlighted by this our index case where diagnosis was delayed for almost a decade partly due to varying opinions by Ophthalmologists. Most patients present with loss of vision, pain, leukocoria and conjunctival congestion [8].

There are some suggested theories on the pathogenesis of medulloepithelioma. Zimmerman [6] hypothesized that medulloepithelioma in children is derived from incompletely differentiated embryonic ciliary epithelium (congenital medulloepithelioma). In rare cases in adults, medulloepithelioma is thought to arise from fully differentiated ciliary epithelium after undergoing non-neoplastic reactive hyperplasia or pseudo-adenomatous hyperplasia. Fuchs [13] believed that adult medulloepithelioma represent neoplastic transformation of hyperplastic ciliary epithelium, triggered by inflammation or trauma. Medulloepithelioma diagnosed in adults could

represent the delayed transformation of a pre-existent retinal anlage [9, 14, 15]. Broughton and Zimmerman [9] have also reported coexistence of persistent hyperplastic primary vitreous in 20% of cases.

Medulloepithelioma can be benign or malignant. Most cases in adults are histopathologically malignant, suggesting a delayed malignant transformation of a pre-existing lesion [12, 15, 16]. Benign medulloepithelioma in adults is detected following decades of gradual growth, eventually manifesting clinically. Medulloepithelioma can rarely arise from the optic disc, iris, and retinal stalk [2, 17-19].

Histopathologically, medulloepithelioma comprises pseudostratified primitive neuroepithelial cells surrounded by hyaluronic acid-rich hypocellular stroma [26] closely resembling the medullary epithelium of the developing neurosensory retina or embryonic neural tube before the fourth month of gestation [11, 26]. The stroma is akin to the vitreous [26] while the neuroepithelial surface facing the hypocellular stroma is lined by a thin basement membrane that corresponds to the internal limiting membrane of the neurosensory retina [26]. Flexner-Wintersteiner and Homer Wright rosettes can be found among the undifferentiated neuroblasts but as compared with those in retinoblastoma, the rosettes in medulloepithelioma, are often larger and more cellular [26]. Features more specific to medulloepithelioma are neuroepithelial tubules and the absence of calcification [26]. Although medulloepithelioma is often said to arise from the region of non-pigmented ciliary body epithelium, foci of intrinsically pigmented tumour cells are relatively common [9, 20, 26].

Based on histopathological findings, intraocular medulloepithelioma is classified as nonteratoid or teratoid, and benign or malignant [6, 9]. Nonteratoid medulloepithelioma comprises purely primitive medullary epithelium. Teratoid medulloepithelioma exhibits heteroplastic elements, commonly mature hyaline cartilage. Sometimes neuroglia (brain-like tissue as seen in this index case) or rhabdomyoblasts (striated muscle) may be seen in addition to the proliferation of the neuroepithelial elements [6, 9, 20, 26]. Occasionally, the entire tissue may be comprised of heteroplastic elements making it nearly indistinguishable from teratoma, sarcoma, or choristoma.

Malignant medulloepithelioma is diagnosed based on four features as described by Zimmerman et al [9]. These features include 1. Retinoblastoma-like elements (sheets of neuroblastic cells among the cords) with or without rosettes. 2. Sarcoma-like elements 3. Pleomorphism and high mitotic index 4. Invasion into adjacent uvea, lens, sclera, cornea, optic nerve, or orbit. All of these features are present in this index case thus fulfilling the criteria for diagnosis.

Immunohistochemical markers have different patterns of reactivity depending on whether the tissue of interest is neuroepithelial or heteroplastic. The nonteratoid component is typically positive for vimentin and neuron-specific enolase [17, 27, 28]. Limited and conflicting results have been observed for chromogranin, synaptophysin, glial fibrillary acid protein, S100 protein, and HMB-45 [17, 27-29]. Immunohistochemistry for pan-cytokeratin and cytokeratin (CK) 18, with no reactivity for CK7, CK20, and epithelial membrane antigen has been described [27]. In large case series of medulloepithelioma in the literature, 50-63% of tumours were nonteratoid (10-31% benign and 19-40%malignant) and 38-50% were teratoid (0-31% benign and 19-50% malignant) [9, 12, 20, 21].

The most common malignant features are high mitotic activity and retinoblastoma-like differentiation, both features were also seen in this index case [20]. The distinction between benign and malignant tumours may be blurred and it is postulated to represent a spectrum rather than two distinct entities [8]. The fact that adults are more likely to present with malignant tumours might also represent a natural progression of the disease [29].

Patients very often present many months after the first appearance of symptoms [8]. Medulloepithelioma is often misdiagnosed as cataract, glaucoma and uveitis, representing the secondary manifestations of the disease [30, 31] and about 20% of cases have been said to be associated with persistent foetal vasculature (PFV) or persistent hyperplastic primary vitreous (PHPV). In this case, the initial clinical impression was that of a staphyloma of unknown aetiology. Usually, patients are treated for these wrongly diagnosed conditions for a long time, before undergoing surgical intervention as in the case of our patient who sought medical care for eight years before a correct diagnosis was finally made. Zimmerman9 found that up to 20% of cases were misdiagnosed and surgically treated for other conditions.

Local belief systems may also play a role in delayed diagnosis as evident in our case where enucleation of the eye was refused despite the proptosis and loss of vision on that eye.

Unless there is extraocular extension or central nervous system involvement, ocular medulloepithelioma rarely results in metastatic illness or tumour-related death [9, 12, 20, 26]. The prognosis for tumours restricted to the globe is good; 90-95% of them survive for five years following enucleation [32, 33].

Conclusion

We have presented what we believe to be the first case report of a histologically diagnosed malignant ocular medulloepithelioma from Nigeria. There was an 8-year delay in arriving at a definitive diagnosis and this was due to diagnostic challenges and traditional belief systems that prevented the patient and his parents from accepting enucleation and tissue diagnosis at the onset of symptoms.

Author Roles

All authors participated in the review of the patient case notes and made the histopathologic diagnosis.

Authors TEO, IDN and BLA conceptualized the idea of presenting it as a case report.

All authors contributed to the writing and editing of the final manuscript.

Conflict of interest

The authors have no conflict of interest to declare.

Ethical considerations

Verbal and written consent was obtained from the patient for this case report.

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