Case Report

An atypical clinical/radiological presentation of Retinoblastoma in a 4-year-old child: A case report & educational lessons from Syria

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ABSTRACT

Introduction: Retinoblastoma (Rb), the most common intraocular malignancy of children, typically presents with leukocoria or strabismus, and in later stages, the most common sign may be proptosis. Radiological techniques show calcification as an important finding for the diagnosis. This neoplasm can mimic any orbital or ocular disease in its atypical clinical/radiological presentations, which delay the diagnosis leading to high mortality rates.

Case presentation: Here we report a case of a 4-year-old male child who presented to our hospital with ocular pain, edema, and inflammatory signs in the right eye, with no calcification. Clinical examination and radiological techniques suggested a broad spectrum of differential diagnoses, including orbital inflammatory pseudotumor. The patient received intravenous fluids and antibiotic therapy, while awaiting further investigations. He was kept under observation status for days and discharged home with a stable condition. After 6 months, he developed severe painful proptosis with a large extraocular mass. Orbital magnetic resonance imaging showed an orbital mass extending outside the orbit in a non-functional eye. Therefore, right eye exenteration was performed, and pathologic examination revealed the diagnosis of Rb. Adjuvant chemotherapy was applied postoperatively. After 3 months of progressive decline because of distant multiple metastases, the patient died.

Clinical discussion & conclusion: Rb must be considered in the differential diagnosis for any intraocular disease, due to the importance of early diagnosis and management. In this manuscript, we aimed to present a case of Rb with atypical symptoms including ocular pain, edema, inflammatory signs, then proptosis, with no finding of calcification in a Syrian child, highlighting a bunch of educational lessons for healthcare workers in developing countries.

1. Introduction

Retinoblastoma (Rb), the most common intraocular malignancy of children, occurs due to mutation of the Rb1 gene on chromosome 13q14 [1]. Rb is often a highly calcified tumor, typically presents with leukocoria or strabismus, and in later stages, the most common sign may be proptosis [2]. Rb can mimic any orbital or ocular disease in its atypical clinical/radiological presentations, which delay the diagnosis and worsen the prognosis [3]. Delayed diagnosis of more than 6 months from the first clinical sign leads to spreading of Rb from the eye, and a 70% mortality rate in developing countries [4]. Herein, we present a case of a Syrian child with atypical clinical/radiological features, which led to lethal extensive complications.

2. Case presentation

A 4-year-old male child presented with ocular pain and edema in the right eye, within 3 days of evolution. Ophthalmological evaluation; bedside evaluation and slit-lamp examination included ocular annexes and anterior segments, revealed normal intraocular pressure (IOP), eyelids edema, and conjunctival hyperemia. Direct and indirect pupillary reflexes were present, other anterior parts were within normal,
posterior segments were difficult to evaluate due to the patient nonco-operation. The left eye was normal. Computed tomography (CT) of the head and orbit, showed no calcification, nonspecific thickening structures, sclera, and adjacent tissue, with enhanced inflammatory tissues surrounding the optic nerve. Based on the clinical features, and the anatomical patterns. There were many differential diagnoses including orbital inflammatory pseudotumor (OIP), orbital trauma, optic neuritis, etc. Magnetic resonance imaging (MRI) wasn’t performed due to financial constraints. The patient received IV fluids and IV antibiotic therapy, while awaiting further investigations. He was kept under observation status for days and discharged home due to the insistence of the parents. After 6 months, he came back because of a worsening condition, developing severe painful proptosis with a large extraocular mass in the right eye (Fig. 1). The direct and indirect pupillary reflexes were absent and very hard to evaluate. Orbital and brain MRI showed an orbital mass, with high signal intensity on T1-weighted images and low signal intensity on T2-weighted images compared to the vitreous. The mass was developing outside the orbit and growing to involve muscles, optic nerve, and bony socket, extending along the optic nerve sheath to the level of the optic foramen to the anterior part of the cavernous sinus, with sinus effusion, bony destruction, and luxation of the eyeball (Figs. 2 and 3). Based on the MRI findings which were suspicious of Rb, neoadjuvant chemotherapy was performed, but with no response. Lid sparing exenteration was discussed thoroughly with parents. They hardly consented to the surgery, and right eye exenteration was performed. In the pathology report, macroscopic examination revealed a mass with no obvious anatomical signs, covered by skin with central ulceration; its cut surface shows wide infiltration by soft white tissue with areas of hemorrhage and necrosis; all resection margins are involved. Eye & orbital mass; Infiltration by small round blue cell tumor with extensive necrosis. The tumor involves the skin with ulceration. Resection margins are involved by the tumor. Specimen from the posterior orbit; wide infiltration by the tumor involving soft tissues (muscular, adipose, and fibrous tissues) and a fragment of optic nerve tissue. Specimen from upper and lower eyelids; focal infiltration by the tumor in both specimens. Microscopic examination demonstrated Flexner-Wintersteiner rosettes, with poorly differentiated tumor cells, large hyperchromatic nuclei, and numerous mitotic figures (Fig. 4). Tumoral cells were positive for NSE, focal and mild positive for Melanoma Cocktail (Fig. 5). According to these findings, the lesion was diagnosed as Rb. Six cycles of adjuvant chemotherapy (vincristine, carboplatin, and etoposide) were applied postoperatively. After 3 months of progressive decline because of distant multiple metastases to the brain and the right side of the mandible, the patient died.

Fig. 1. Severe proptosis with a large extraocular mass (associated with advanced Rb).

Fig. 2. Axial, coronal, and sagittal post-gadolinium T1-weighted images, respectively. Showing massive enlargement of the intraocular heterogeneous enhancing mass with interruption of the sclera, extrascleral extension, and invasion of the optic nerve. Bony destruction is also noticed.

Fig. 3. Axial, coronal, and sagittal T2-weighted images, respectively. showing luxation of the globe and retro ocular extension with sinus effusion. No invasion of the brain tissue is noticed.

3. Discussion

Rb is the most common eye childhood malignancy [4], typically before the age of 5 in 95% of patients [1]. At early stages, most patients present with leukocoria and strabismus. At later stages, patients may exhibit proptosis, buphthalmos, or hypopyon [1]. Leukocoria is presented in 60-80% of cases, and identified by lay people because of an
patients in our case, the patient's complaints were ocular pain, edema and inflammatory signs which are atypical presentations that led to misdiagnosis of OIP, delaying the correct diagnosis of Rb. The diagnosis of Rb is made early in developed countries while the tumor remains intraocular. However, in developing countries, most cases are diagnosed after a local invasion or distant metastases [2,7]. If intraocular tumors are left untreated, extraocular spreading occurs within 6 months, by an invasion of either the optic nerve or the choroid into the cerebrospinal fluid (CSF), brain, spine, blood, lymph nodes, the soft tissues, or bones [8]. Metastatic Rb is considered to have a poor prognosis and only a few patients survive even after intensive chemotherapy [2,7]. Rb is often a highly calcified tumor. Calcification is more often presented in older children and advanced disease, as a response to necrosis or tissue damage [2]. Using USG, Rb is typically an echogenic irregular retinal mass with focal acoustic shadows, ocular calcifications, and retinal detachment. However, it is not the imaging modality of choice in advanced Rb [8,9]. CT has an 81–96% sensitivity of detection of calcifications in Rb and high specificity. Rb is discernible on CT as a mass of high density compared with the vitreous body, usually calcified and moderately enhanced after iodinated contrast medium administration. However, the sensitivity of CT in the evaluation of optic nerve invasion is very low, and in imaging intraocular soft tissue details are limited [9]. MRI is preferred in Rb because of the risk of radiation exposure (ionizing radiation) with CT imaging [8,10]. The gold standard of Rb evaluation is the MRI of the orbits and brain [8]. It is the technique of choice to evaluate the intraocular tumors, determine disease extent, and its infiltration outside the eye [9]. MRI is the most superior non-invasive method in the detection of Rb optic nerve invasion, as it has an 80% specificity and a 74% sensitivity. Therefore, The European Retinoblastoma Imaging Collaboration (ERIC) released a guideline protocol for using MRI in Rb [10]. In the beginning, CT in our case suggested a broad spectrum of differential diagnoses; there was no finding of calcification, and that made us not think of Rb, especially since the symptoms were atypical, but when the disease progressed, MRI findings and clinical features were consistent with Rb. Rb is one of a few tumors which can be diagnosed and treated without histological confirmation via biopsy [2,8]. Biopsy of Rb is rarely required, as it can induceextraocular spreading and seeding [2]. The gross appearance of Rb at the cut section of the eye depends on the stage of the tumor. It is presented with a white, encephaloid, or brain-like appearance, yellow necrotic areas, and chalky areas of calcification [11,12]. Under the microscope, Rb may demonstrate large areas of necrosis and multifocal calcification. The viable tumor cells are small, hyperchromatic, and active cleavage with a high nuclear to cytoplasmic ratio [12]. These cells surround blood vessels and form a characteristic pseudorosette. We also find Flexner-Wintersteiner rosettes, which contain cells with projecting photoreceptors [11]. In our case, the pathological study was made after lid sparing exenteration, and it was the way of a definitive diagnosis of Rb. Treatment decision depends on many factors including the prognosis of vision, age of the patient, location and size of the mass, and the presence or absence of seeding. Rb often needs a combination of therapies to optimize patient care [11]. The treatment goals are first, saving the patient’s life, and second, saving the vision. There are many treatment options like enucleation, laser photocoagulation, cryotherapy, thermotherapy, chemothermotherapy [7]. Enucleation is the definitive treatment of Rb. The frequency of enucleation gradually decreased due to improvement in other treatment methods [1]. Currently, alternative approaches are being tested to avoid the toxicity of radiotherapy and chemotherapy and the risk of secondary tumors [7]. Our patient was treated with exenteration, and chemotherapy, as he had a very high-risk metastatic Rb due to the delay in diagnosis and treatment. These treatment methods did not stop the progression of the disease and the patient died. Finally, we have to mention that this work has been reported in line with the SCARE 2020 criteria [13].

4. Conclusions

No child with Rb should lose his chance of a cure, or die from metastases, because of delayed diagnosis and treatment. The management of Rb should be a team approach by the parents, pediatric oncologists, ophthalmologists, and radiologists. They should retain a high index of suspicion for Rb in all children with intraocular disease. The picture described in this case report could be a resource for teaching and learning, since it represents a healthcare encounter involving a real patient with a real clinical problem in a developing country, that offers a lens in which to view single episodes of care to facilitate the understanding of a larger body of evidence in developing countries, which may be reflected in our guidelines in third world (Table 1).

Author agreement statement

We the undersigned declare that this manuscript is original, has not been published before, and is not currently being considered for publication elsewhere. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We understand that the Corresponding Author is the sole...
A summary of the educational lessons from this case.

The diagnosis was missed, and Rb was diagnosed only after 6 months in a very advanced stage. Why is that?

- Atypical symptoms (Ocular pain, edema and inflammatory signs.)
- Atypical findings on USG and CT (No finding of calcification despite Rb shows calcification in over 90% of cases).
- Parents in the developing world where there is no awareness about cancer, the importance of early diagnosis, and how much losing an eye is better than losing a life.
- The features of OIP overshadowed the correct diagnosis of Rb, and parents put additional pressure not to accept any diagnosis related to malignancy.

So what?

- Rb must be considered in the differential diagnosis for any intraocular disease, due to the importance of early diagnosis and management.
- The management of Rb should be a team approach by the parents, pediatric oncologists, ophthalmologists, and radiologists.
- The consequences of false positive and false negative diagnoses in this disease should be well understood.
- Despite the distinct features of Rb, and the aid of diagnostic imaging modalities, histopathological examination may be the only way to a definitive diagnosis of Rb.

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Declaration of competing interest

The Authors declare that there is no conflict of interest.

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Abbreviations

Rb Retinoblastoma
IOP Intraocular pressure
OIP Orbital Inflammatory pseudotumor
USG Ultrasonography
CT Computed tomography
MRI Magnetic resonance imaging
CD Cluster of differentiation
IV Intravenous
NSE Neuron-specific enolase
PFV Persistent fetal vasculature
FEVR Familial exudative vitreoretinopathy
IRSS International Retinoblastoma Staging System
IIRC International Intraocular Retinoblastoma Classification
ICRB Intraocular Classification of Retinoblastoma
TNM tumor nodes metastasis
CNS The central nervous system
CSF Cerebrospinal fluid
ERIC The European Retinoblastoma Imaging Collaboration
H&E Hematoxylin and eosin

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.103830.

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