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Retinoblastoma metastasis

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Retinoblastoma metastasis: A Study at Tertiary care centre in South India

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Objective: Retinoblastoma is the most common primary ocular malignancy in children. Bone marrow involvement by solid tumors implicates advanced disease and a bad prognosis. Bone marrow aspiration and biopsy, are performed routinely for staging for small round cell tumors and unexplained cytopenia in other solid tumors . It is important to rule out bone marrow involvement before planning for any definitive, curative treatment.

Materials and Methods: This was a retrospective observational study of bone marrow involvement by, Small round cell tumors / solid tumors and their hematological manifestation, especially the Retinoblastomas.

Results: Evaluation of Bone marrow evaluation during the past 7 years, in solid malignancies revealed. Out of 772, 342 were pediatric cases and 430 were adult cases. Bone marrow was involved in 82 patients. In children, bone marrow involvement was present in 42 cases, and in adults, bone marrow involvement was diagnosed in 40 cases. Neuroblastoma was the most common malignancy, which involved the bone marrow in pediatric cases, followed by Ewing's sarcoma& retinoblastoma, Out of 16 cases there were 6 cases of Retinoblastoma involving marrow.

Conclusion: The small round blue cell tumors are the major cause of bone marrow involvement in pediatric, Retinoblastoma metastasis is less common in advanced countries, however not so rare in developing countries A diligent and exhaustive search for metastatic cells in Bonemarrow helps in treatment and prognosis, Use of immunohistochemistry markers on bone marrow biopsies results in higher detection rate, also aids in picking very few neoplastic cells, thereby helps in detecting early metastasis. RB treatment is to save the patient's life, salvage of the eye and vision are secondary goals and need a multidisciplinary team approach.

Keywords: Retinoblastoma, Bone marrow, early diagnosis, intraocular, Leukocoria

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Introduction

Malignancies that exhibit peaks in incidence, in children younger than age 10 years, ALL, neuroblastoma, Wilms tumor, hepatoblastoma, retinoblastoma, rhabdomyosarcoma, Ewing sarcoma etc Histologically, many of the malignant non-hematopoietic pediatric neoplasms are unique.

In general, they tend to have a more primitive (embryonal) undifferentiated appearance and are often characterized by sheets of cells with small, round nuclei, childhood tumours have been collectively referred to as their malignant small round blue cell tumors, due to their primitive histologic appearance.[1],[2]

The most common paediatric intraocular malignant neoplasm is retinoblastoma[3]. Assessing the bone marrow status of newly diagnosed patients is essential for management and prognosis. Here we discuss 6 such cases of Retinoblastoma involving bone marrow and their clinical presentation, management and prognosis.

This study aimed to give an overview of the disease along with the utility of bone marrow examination in cases of retinoblastoma. Early diagnosis, advancements in management and follow-up of the cases have resulted in improved eye and vision salvage. Retinoblastoma(RB) is an intraocular malignant neoplasm which is most commonly seen in children.[3]

Cell of origin neuronal progenitor. Around 40% of retinoblastomas have an inherited germline mutated RB gene allele. It is usually diagnosed by 5 years of age[3].

The overall survival rate in patients diagnosed early and with localized intraocular disease exceeds 95% however, in developing countries delayed diagnoses and treatment are common and may lead to extra-ocular and distant metastases.

The sites of distant metastases in Retinoblastoma include the central nervous system, bone marrow, bone, lymph nodes, and other organs [4] Older age at diagnosis and advanced tumor stage are independent risk factors which are associated with the worst prognosis [4,5] Here we present 16 such cases of Retinoblastoma. 6 cases came to our institute at an advanced stage of disease with bone marrow involvement at presentation.

These cases presented to our hospital with Leucoria, and had normal haematological parameters in most of the patients, This study aimed to give an overview of clinical presentation, diagnosis, treatment and prognosis.This is the study of Retinoblastoma cases, metastasis to bone marrow, over 7 years (2006-2013), from a regional cancer centre in India.

Materials and Methods

In Kidwai Cancer Hospital, Bengaluru, India, between January 2006 to January 2013, all suspected nonhematological malignancies, received in our department, which involved marrow were evaluated. Lymphoma were excluded in this study.

Haemogram details were reviewed. Bone marrow was obtained from the posterior iliac crest by Jamshidi needle. Bone marrow smears and peripheral smears and stained by Romanowsky stains, Bone marrow biopsies were stained with hematoxylin and eosin. Immunohistochemistry followed in a few cases. Patient's name, age, gender, diagnosis, and clinical, radiological findings were recorded. Children age<14 years. The bone marrow was considered to be 'involved by the tumor' if tumor cells were detected in bone marrow aspirate, biopsy, or both.

Results

Results: bone marrow examinations, of suspected SRCT /solid malignancies patients were evaluated. Out of 772 total cases, 342 were pediatric cases and 430 were adult cases. (Table 1)

Table 1: Distribution of bone marrow involvement among pediatric patients

	number of cases	Number of positive cases
Pediatric cases	342	42
Adult cases	430	40
Total	772	82

Bone marrow was involved in 82 patients(fig1). Bone marrow involvement was present in 42 cases, in children. Neuroblastoma was the most common malignancy, which involved the bone marrow among pediatric cases(Table 2), followed by Ewing's sarcoma& retinoblastoma, [Table2]Out of 16 cases of retinoblastoma only 6 cases showed bone marrow metastasis. .Among adult solid tumors, involving bone marrow, the breast is common in women and prostatic carcinoma in men.

Table 2: bone marrow involvement of RB among pediatric patients

Diagnosis	Number of cases
Neuroblastoma	18
Ewing's sarcoma	14
Retinoblastoma	6
Rhabdomyosarcoma	4
Total	42

Male preponderance was noted. The most common manifestation of Retinoblastoma is Leukocoria (fig1,2,3,4),

Figure: 1,2,3,4 showing Leukocoria. , a reflection of light by the white mass in the fundus

Other manifestations are strabismus, painful blind eye and loss of vision

Table 3: Clinical Presentation among Retinoblastoma patients

common presenting features of RB	Achyut	Current study
Leukocoria	56%	80%
strabismus	20%	7%
Red painful eye	7%	3%
Poor vision	5%	5%
Mydriasis,cellulitis,iridis,hyphema etc	5%	

Anaemia was common, leucopenia/neutropenia and thrombocytopenia were seen in few. Pancytopenia was found in 2 children

On H&E 20x undifferentiated appear as small round cells with hyperchromatic nuclei (fig 5.)

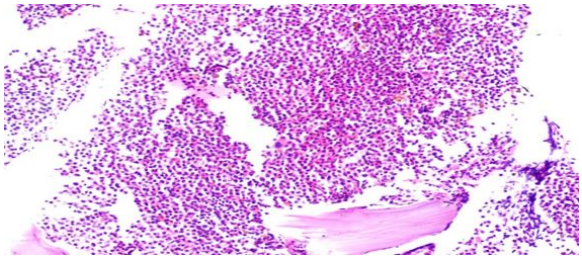

Figure 5: H&E 20x undifferentiated appear as small round cells with hyperchromatic nuclei

As our institute is a referral centre, we couldn't do a histopathological risk factor analysis as the entire set of slides was not available.

Discussion

Paws described retinoblastoma as early as 1597 discovery of an ophthalmoscope in 1851 facilitated the diagnosis of what initially was thought as glioma of the retina by Virchowin 1864 however in 1891 Flexner and 1897 Wintersteiner named it as neuroepithelioma due to rosettes.[The most common manifestation of Retinoblastoma is Leukocoria, other manifestations are strabismus, painful blind eye and loss of vision. Moderately advanced lesions usually present with Leukocoria due to the reflection of light by the white mass in the fundus.[3]

Early diagnosis is essential to prevent the spread to other adjacent structures like the optic nerve, orbit, brain and systemic metastasis. Retinoblastoma, familial / sporadic. All cases of Bilateral retinoblastomas involve germinal mutations.

Tumor growth can be Endophytic,tumor grows into the vitreous cavity, exophytic in which tumor grows towards sub retinal space, or it could be a diffuse infiltrating tumor.[3],[4] In 1971 Knudson proposed the two-hit hypothesis. In hereditary RB the initial hit is a germinal mutation, found in all cells, and the second hit in somatic retinal cells leading to RB In unilateral retinoblastomas 15% are caused by germinal mutations, while rest, the majority are sporadic Pathology of retinoblastoma both hereditary sporadic are identical. Tumor may contain both differentiated and undifferentiated elements, on H& E.undifferentiated appear as small round cells with hyperchromatic nuclei. Well-differentiated tumors have Flener-Wintersteiner rosettes, arrangements of a single layer of tumor cells around a lumen .dystrophic calcification might be seen. The diagnosis of Retinoblastoma is done by examination of the eye under anesthesia. Imaging of the brain and orbits is also done to evaluate the extent of the spread of tumour. Bone marrow examination and cerebrospinal fluid (CSF) analysis are done to rule out the systemic spread in cases of extraocular Retinoblastoma. The most common metastatic site of RB is the intracranial area, accounting for approximately half of cases. Bone is the second most common site. [4],[5],[6],[7]

.Anaemia was the common abnormality due to bone marrow involvement, the leucopenia/neutropenia and thrombocytopenia followed respectively. Pancytopenia was found in 2 children. Normal blood picture, in the majority of patients, confirmed hematological abnormality may not be always present in bone marrow metastasisRetinoblastoma has to be differentiated from, endophthalmitis retinal dysplasia retinal detachment, vitreous haemorrhage, Coats' disease, and toxocariasis [8], [9] The incidence of retinoblastoma is constant worldwide at 1 in every 16,000 live births. Retinoblastoma is the most common eye cancer in children. It arises in the developing retina, part of the central nervous system (CNS). Thus, retinoblastoma is a CNS cancer viewable from the outside. Medical diagnosis of retinoblastoma is based on the clinical features of the tumors visible in the eye upon dilation of the pupil. This differs from the diagnosis of other cancers, where histological confirmation via biopsy is usually required. Biopsy of retinoblastoma is not recommended, as it can induce seeding and extraocular spread along the needle tract.[3],[8]

In this study, we found neuroblastoma as the most common malignancy metastasizing to bone marrow among pediatric cases. Neuroblastoma was followed by Ewing's sarcoma and retinoblastoma, there were 16 cases of Retinoblastomas, and marrow involvement was seen in 6 cases. All of them belong to paediatric age group and presented with bone marrow involvement at diagnosis. Bone marrow Aspiration and Biopsy showed atypical cells in clusters with hyperchromatic nucleus and scant cytoplasm. Immunohistochemistry was done and it showed Synaptophysin and NSE expression. Patients with RB metastasis have a poor prognosis[10], [11],[12],13]. RB metastasis is an important cause of death in RB patients. Treatment options for retinoblastoma include enucleation, Chemotherapy by various routes of intravenous, intra-arterial, intravitreal, and intracameral infusion and focal therapies with cryotherapy, plaque radiotherapy and laser photocoagulation/thermotherapy [3]. Early stages of Retinoblastoma have a good prognosis, whereas that of metastatic cases is very poor. The high survival rate of Retinoblastoma patients in developed countries is mainly because of early identification and standardization of management of these cases. Imaging studies like CT and MRI give detailed evaluation, including the size of the lesion, and the extent of invasion to the adjacent soft tissue. Also in addition a Radionuclide bone scan or PET/CT have been used to screen for bone metastasis.

On H&E tumor differentiation & extent of ocular involvement should be noted. Can be classified as differentiated, presence of Flexner-Wintersteiner rosettes and undifferentiated appear as small round cells with hyperchromatic nuclei. Histopathological Risk Factors in Retinoblastoma include invasion into the anterior chamber, angle, iris, ciliary body, choroidal invasion, optic nerve invasion, invasion of the sclera, and any extraocular spread. Bone marrow biopsy were reviewed for any metastasis.IHC helps in confirming the neoplastic cells in the marrow As our institute is a referral centre, we couldn't do a histopathological risk factor analysis as the entire set of slides was not available. Hence bonemarrow metastasis was diligently screened and IHC were done whenever necessity arose. Neuron-specific enolase (NSE) is an important marker of neurogenic tumors which can be used as a tumor marker for Metastatic cases of Retinoblastoma[13].

Differential diagnosis includes other small round blue cell tumours like Ewing's sarcoma. The probability of a second primary tumour is higher in cases of hereditary Retinoblastoma if radiotherapy is used for treatment.[14]) None of the cases in the current study, had prior radiotherapy history.

A thorough clinical evaluation, along with B scan ultrasonography aids in diagnosis.[14],[18] CT/MRI gives the detail of intra/extracranial spread. Intraocular RB is treated by cryotherapy trans scleral thermos therapy, external beam radiotherapy, enucleation etc. Treatment of metastatic Retinoblastoma is challenging as it has poor prognosis, low survival and high recurrence.

Systemic Chemotherapy along with surgery, intrathecal chemotherapy, radiotherapy, and hematopoietic stem cell transplantation is considered effective in the management of such cases[16.17,18]. Early detection of retinoblastoma, standardized treatment protocols and long-term follow-up are essential to improve the prognosis.

Conclusion

The risk of death in patients with Retinoblastoma is increased in those who present with metastatic disease.A diligent and exhaustive search for metastatic cells in Bonemarrow helps in treatment and prognosis.

Retinoblastoma though not frequent, are not so rare. A diligent search of metastatic cells and the Use of immunohistochemistry markers on bone marrow biopsies may result in a higher detection rate primary goal of RB treatment is to save the patient's life, salvage of the eye and vision are secondary goals, need a multidisciplinary team approach.

Reduction in the rate of systemic metastasis by identification of high-risk factors and appropriate adjuvant therapy improves survival.

Abbreviations: SRCT: small round cell tumours, RB: Retinoblastoma

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