

Research Article

Paradigm of Bone Marrow Metastasis in Retinoblastoma

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Abstract: Introduction: Retinoblastoma is most common pediatric ocular malignancy. Majority of patients presented with unilateral disease. Infiltration to other organs is common with bone marrow being one of the most common organ involved.

Methodology: This study was conducted at Pakistan Institute of Medical Sciences Islamabad for a period of one year. A total of 47 known patients of retinoblastoma were included in study. All patients underwent bone marrow biopsy for evaluation of infiltration.

Results: Out of 47 patients, 32 (68.1%) were male and 15 (31.9%) were female (ratio 2.13:1). 37 (78.7%) patients were unilateral and 10 (21.3%) were bilateral. Bone marrow infiltration was present in 14 (29.78%) cases.

Conclusion: Bone marrow is among most common sites of involvement in patients with bone marrow biopsy. Distant metastatic involvement has great impact on treatment and overall survival of patients.

Keywords: Retinoblastoma, Bone marrow, Metastasis, Malignancy, RB gene, Malignancy, Ocular.

INTRODUCTION

Retinoblastoma is among most common ocular malignancy in pediatric age group. It is responsible for about 1% of deaths from cancer in patients up to 15 years of age [1, 2]. In 60% patients, retinoblastoma is unilateral and 40% were bilateral [3]. “Two – hit” model was described two events for conversion of retinal cells into malignant cells. The mutation causing the event is inherited and is more likely to be present in all cells of the body. The second ‘hit’ event usually results in loss of remaining normal allele and takes place within specific cells in the retina or cells with dysregulation of cell cycle and ultimately inadequate entry in S phase [4]. Retinoblastoma usually presents as leukocoria or strabismus. In the later stage of retinoblastoma, it may present as hypopyon, proptosis or buphthalmos. The main pathological genetic problem is loss of function mutation in *RBI* gene on chromosome 13q [5, 6]. *RBI* gene functions as tumor suppressor gene which is essential for adequate cell cycle exist in progenitor cells in retina which are proliferating. It is also required for adequate maturation in differentiation of rods. If *RBI* gene is absent, the progenitor cells will be divided continuously and maturation of the rods will not take place [7, 8]. Retinoblastoma is associated with an increased risk of secondary tumors. Metastasis to various organs e.g. bone marrow is associated with retinoblastoma and it is related to various ocular, pathological and outcome factors in treatment [9, 10].

Bone marrow is one the commonest site which is involved in

metastasis and its detection is of great importance for staging of tumor spread. Metastasis influences the response treatment response, survival and reduced hematopoiesis [11]. In this study, we evaluated the frequency of bone marrow infiltration in patients with retinoblastoma.

MATERIALS AND METHODS

This was a cross-sectional study, conducted at Department of Pathology, Pakistan Institute of Medical Sciences for the period of one year (January 2016 to December 2016). A total of 47 pediatric patients who were known cases of Retinoblastoma were included in the study. After full consent, all patients underwent bone marrow biopsy for staging of the disease. Patients on chemotherapy/radiotherapy were excluded from the study. All basic hematological markers (e.g. CBC, Retics) were evaluated in the patients. Bone marrow aspiration was performed on patients from tibia (for patients less than 2 years) and posterior iliac crest (for patients more than 2 years), under local anesthesia. Aspiration was performed using 16G LP needle and trephine was performed using 14g x 40mm trephine biopsy needle. Slides were prepared using May – Grunwald – Giemsa stain and examined for presence of malignant cells. Data was analyzed using statistical software SPSS version 21. Quantitative variables like age and other hematological markers are presented as mean \pm standard deviation. Qualitative variable like gender, retinoblastoma type and results of bone marrow biopsy are expressed as frequencies with percentages.

RESULTS

A total of 47 patients were selected for the study. Out of 47 patients, 32 (68.1%) were male and 15 (31.9%) were female.

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Male to female ratio was 2.13:1 (Fig. 1). Age of patients was ranged from 6 months to 11 years and the mean age was 6.1 ± 1.86 years. 37 (78.7%) cases were unilateral and 10 (21.3%) were bilateral (Fig. 2). Infiltration was present in 14 (29.78%) cases, while 33 (70.21%) did not show any tumor cells. Hemophagocytosis was present in 15 (31.9%) cases. 20 cases (42.6%) showed increased lymphocytes on bone marrow (Fig. 3). Basic hematological parameters were evaluated by CBC and reticulocyte count. Mean hemoglobin was 10.36 ± 1.53 g/dL, mean MCV was 69.64 ± 7.45 fL, mean RBC count was 4.46 ± 0.76 millions, mean hematocrit was $33.3 \pm 3.33\%$, mean WBC count was $13.55 \pm 4.18 \times 10^9/L$, mean RDW $17.81 \pm 2.47\%$, mean platelet count $484.61 \pm 119.30 \times 10^9/L$, mean neutrophil count $45.70 \pm 13.55\%$, mean lymphocyte count $44.74 \pm 13.55\%$, mean monocyte count $4.53 \pm 2.96\%$, mean eosinophil count $4.97 \pm 4.3\%$ and mean reticulocyte count $1.28 \pm 0.84\%$ (Table 1).

Table 1. Hematological Parameters in Patients with Retinoblastoma (n = 47).

	Mean ± Standard Deviation
Age (years)	6.1 ± 1.86
Hemoglobin (g/dL)	10.36 ± 1.53
MCV (fL)	69.64 ± 7.45
RBC (millions)	4.46 ± 0.74
HCT (%)	33.30 ± 3.33
WBC (x 103/L)	13.55 ± 4.18
Platelets (x 109/L)	484.61 ± 119.30
RDW (%)	17.81 ± 2.47
Neutrophils (%)	45.70 ± 13.68
Lymphocytes (%)	44.74 ± 13.55
Monocytes (%)	4.53 ± 2.96
Eosinophils (%)	4.97 ± 4.30
Retics (%)	1.28 ± 0.844

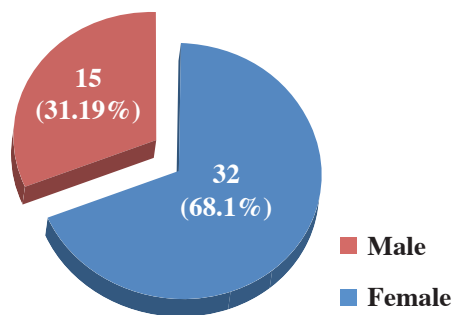


Fig. (1). Gender Distribution (n = 47).

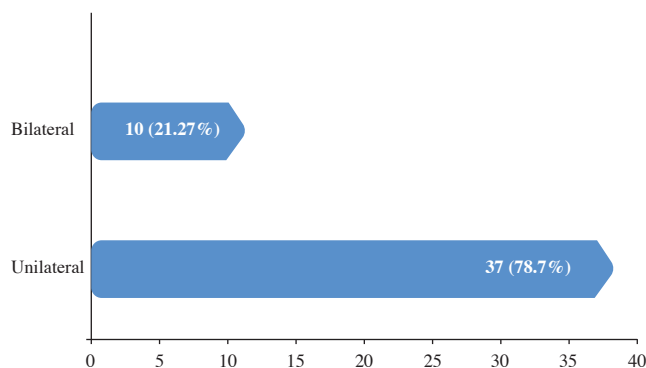


Fig. (2). Type of Retinoblastoma (n = 47).

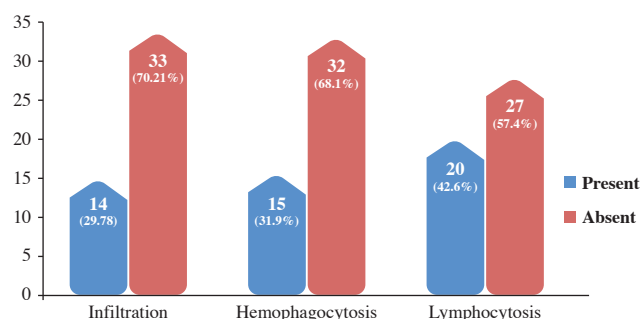


Fig. (3). Bone Marrow Biopsy Examination in Patients with Retinoblastoma (n = 47).

DISCUSSION

Retinoblastoma is among most common intraocular tumor of childhood. It makes up approximately 4% of all childhood malignancies [12]. Bone marrow is a common site for secondary involvement in patients with retinoblastoma, followed by bones, liver, and other organs [13]. Various studies have been done to see the paradigm of infiltration in retinoblastoma. Khurram *et al* performed a study in 2011. He showed that 41.2% patients were bilateral, and 62.74% patients presented with advanced stage disease [14]. These result are different from our study, in which majority of patients were unilateral and presented in primary stage. Arif *et al* presented a study in Peshawar. He included 80 known cases of Retinoblastoma. In his study 25% patients presented with metastasis [15]. Khurshid *et al.* performed a study in patients with retinoblastoma. He showed that 90% patients had unilateral disease, and 10% patients presented with bone marrow infiltration [16]. Hu *et al.* showed his study on 24 patients with retinoblastoma. In his study 75% were unilateral, but only 1 case (4.16%) showed bone marrow infiltration [17]. Zhang *et al.* did a study on 92 patients with retinoblastoma, with 83.69% patients presented with unilateral retinoblastoma [18]. Selistre *et al.* showed the data of patients of retinoblastoma in Brazil. He included 140 patients in his study, out of which 65% patients were unilater-

al, and 10.7% patients showed metastatic infiltration at various sites [19]. Majority of studies were in favor of our study with majority of patients having unilateral disease. Bone marrow biopsy is one of the common sites involved in patients with retinoblastoma, having significant impact of treatment and overall survival [20]. Hematological parameters, especially hemoglobin level and MCV decreased. This may be explained by role of RB gene involved in the process of erythropoiesis, which may include the role of retinoblastoma protein – interacting zinc finger protein (RIZ)/ positive regulatory domain methyl transferase (PRDM2) having tumor – suppressive properties. Deletion of loss of heterozygosity of this gene is present in various human malignancies, including both hematological and malignant lymphoma [3].

CONCLUSION

Majority of patients presented with unilateral retinoblastoma with significant number of patients having bone marrow infiltration. Early detection of metastatic involvement may be beneficial in treatment modalities. With proper and early investigation in patients with retinoblastoma, disease can be diagnosed before involvement of other organs.

CONFLICT OF INTEREST

Declared none.

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