A Case Series

Metastatic retinoblastoma- A case series

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ABSTRACT
Background: Retinoblastoma (RB) is one of the common tumors of the childhood which has variable local and distant metastases. There are different factors which can predict the possibility of metastasis and guide the further management. **Case Series:** Out of the 78 bone marrow procedures performed during the year 2022, seven bone marrows aspirations (BMA) were performed in the cases of RB. Complete blood count (CBC), peripheral blood smear (PBS), BMA and cerebrospinal fluid (CSF) cytology done in the cases of RB were reviewed. Out of the seven BMA, two cases showed presence of metastasis. CSF cytology revealed no atypical cells in all the cases. **Conclusion:** BMA and CSF cytology are simple procedures and both can provide valuable information. When all the above mentioned tests and procedures are correlated, they can help in guiding the treatment.
Key words: Retinoblastoma, Bone marrow aspirate, Bone marrow biopsy, CSF cytology, Metastasis

INTRODUCTION

Retinoblastoma (RB) accounts for nearly 3% of paediatric tumors and is one of the common tumors involving bone marrow after neuroblastoma, rhabdomyosarcomas and Ewing's sarcoma.[1,2]Bone marrow examination is usually done to diagnose disorders of haematopoiesis. In adult tumors, it is done for staging purposes.[3,4]For paediatric tumors like RB, it is an important tool for diagnosis, staging and treatment management. Indeed, bone marrow examination is a simple test that can provide valuable information and has therapeutic implications. In this case series of RB, we have studied metastasis in bone marrow and cerebrospinal fluid.

CASE SERIES

This is an observational study, where we have reviewed BMA and CSF cytology of paediatric patients with RB during the year 2022 (January to December). Of the total 78 bone marrow aspirates (BMA) performed during the year, we got seven BMA done in the cases of RB. Patients with age less than 12 years were considered to be paediatric. Clinical, radiological and haematological findings were recorded. Complete blood count (CBC) comprising measurement of haemoglobin, leucocyte count and platelet count and peripheral blood smear (PBS) examination was done. Age, gender, unilateral or bilateral involvement, presenting symptoms of all the seven cases were recorded. Bone marrow aspiration was performed using Salah BMA needle and aspirate was taken from posterior superior iliac spine (PSIS). Bone marrow biopsy was not performed in any of the cases. Both the BMA and PBS were stained with Leishman stain. A careful examination of the PBS and BMA was done to find clusters of atypical cells and if present were labelled as "positive for metastasis" and if not then it was labelled as "negative for metastasis". Refer to figures 1 and 2 which show clusters of atypical cells in Leishman stained BMA. CSF was collected from lumbar puncture and sent immediately for reporting. All these features are formulated in table no 1.

Case 1: This was a two years male child with unilateral involvement (left), came with the complaints of orbital cellulitis, swelling, congestion, discharge and white eye reflex since eight months. Radiology showed mass lesion in the orbit. PBS showed microcytic hypochromic anaemia with normal leucocyte and platelet counts. BMA showed normal

cellularity and was negative for metastasis. CSF sample was not received.

Case 2: A four years female came with swelling, redness, watering and white opacity in the right eye since four months. Radiology showed soft tissue mass with multiple calcific necrotic foci. PBS showed moderate anisopoikilocytosis, with predominant microcytic hypochromic red cells and few normocytic, normochromic red cells. Leucocyte and platelet counts were normal. BMA showed normal cellularity. Both BMA and CSF were negative for metastasis.

Case 3: This was six years old male, the oldest patient, with bilateral involvement. Patient had whitish opacity in the right eye since three years of age and left eye was involved later after two years. Patient complained of pain and redness in both the eyes since three to four days. Radiology revealed total retinal detachment and partial calcification in the right eye while left eye had extensive calcification with no normal structures discernible. PBS showed predominantly normocytic normochromic red cells with few macrocytes. Leucocyte and platelet counts were within normal limits. BMA was too dilute to be commented upon. CSF cytology was negative for metastasis.

Case 4: A three years old male came with the complaints of pain, redness and swelling in the left eye since one month. Radiology revealed diffuse involvement of the left eye with specks of calcification. PBS examination showed predominant normocytic normochromic red cell population with leucocyte and platelet counts being normal. BMA was dilute however showed many clusters of atypical cells and was labelled as positive for metastasis. CSF sample was not received.

Case 5: A one and half years old male presented with swelling of left upper eyelid with sticky discharge. It was associated with white opacity. Right eye appeared asymptomatic. On radiology, both the vitreous cavities were filled with mass lesion and diffuse calcification. Thus, there was bilateral involvement. Normocytic normochromic red cells were seen on PBS. Both the leucocyte and platelet counts were normal. BMA had low cellularity with presence of many cohesive clusters of atypical cells and was positive for metastasis. CSF cytology was negative for metastasis.

Case 6: An eight months old male, the youngest patient, presented with diminution of vision, swelling and congestion since two months. Radiology showed calcified lesions in both the globes, suggestive of RB. PBS showed predominant normocytic normochromic red cells with normal leucocyte and platelet counts. Both BMA and CSF were negative for metastasis.

Case 7: A four years female came with complaints of diminution of vision in both the eyes since one year. There was history of trauma to the left eye preceding the symptoms. Radiology confirmed bilateral involvement as both the globes showed well circumscribed masses in the posterior chambers of the eyes.PBS showed normocytic normochromic red cells with normal leucocyte and platelet counts. BMA showed low cellularity and was negative for metastasis. CSF sample was not received.

Table no 1: Various clinical and pathological features in retinoblastoma patients.

Sr.no	Age	Gender	Involvement	Bone marrow Aspirate	CSF
Case 1	2 years	Male	Unilateral (left)	Negative for metastasis	Not received
Case 2	4 years	Female	Unilateral (right)	Negative for metastasis	Negative for Metastasis
Case 3	6 years (oldest)	Male	Bilateral	Diluted bone marrow, no definite opinion possible	Negative for Metastasis
Case 4	3 years	Male	Unilateral (left)	Positive for metastasis	Not received
Case 5	1.5 years	Male	Bilateral	Positive for metastasis	Negative for Metastasis
Case 6	8 months (youngest)	Male	Bilateral	Negative for metastasis	Negative for Metastasis
Case 7	4 years	Female	Bilateral	Negative for metastasis	Not received

Figure no 1 and 2: Leishman stained bone marrow aspirate showing clusters of atypical cell- positive for metastasis.

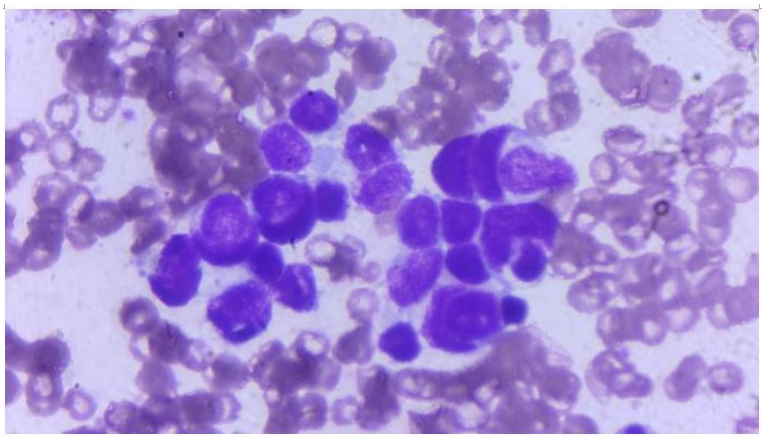

Figure 1

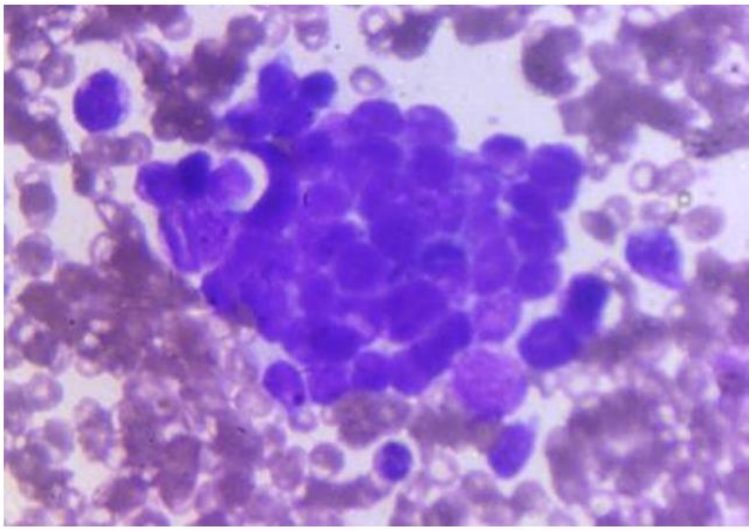

Figure 2

DISCUSSION

RB is one of the most vividly studied tumors and Knudson's two hit hypothesis is a breakthrough in the understanding of tumorigenesis.[1]Radiological investigations like (Computerized Tomography) CT scan and (Magnetic Resonance Imaging) MRI provide valuable inputs in the diagnosis of RB. MRI is superior to CT scan as it provides discrete soft tissue involvement and avoids exposure to harmful ionizing radiation.[5,6] RB is associated with calcification which is invariably picked up on radiology. Positron Emission Tomography (PET) scan helps to detect tumor metabolism in the bone and now a days combination of MRI and PET scan is widely used for early diagnosis of tumor metastasis.[5,7] So, based upon these observations RB was diagnosed using clinical and radiological features without any difficulty. There are various concepts and theories that have elucidated the role of mesenchymal cells of the bone marrow, regulatory T cells etc. in building a protective and growth promoting tumor microenvironment.[8]According to Stephan Paget tumor metastasis follows the soil and seed theory where bone marrow is the 'soil' component which provides nutrition and the tumor cells are the 'seeds'.[7,8] Metastasis in RB accounts for <5 % and mainly occurs through direct invasion or via haematogenous or lymphatic channels.[9] Metastasis is commonly associated with relapse and high grade histological features like Optic nerve, choroidal and anterior segment invasion.[10,11] Hence, it is always better to rule out metastatic spread. Thus, BMA and CSF cytology is useful for staging and therapy.As stated in the literature, the most common presenting sign and symptom of RB is leukocoria and strabismus.[1,11] Similarly, our cases also presented with these symptoms. In addition, swelling, watering and diminution of vision were also seen. Hereditary RB have early onset and are usually bilateral while non-hereditary or sporadic RB are mostly unilateral with late onset.[12,13] Three of our cases were unilateral and the remaining four cases were bilateral. Generally, this tumor does not have any gender predilection.[9,13] But in our study, males were affected more than females.There were no serious fluctuations in haematological parameters except for anaemia,

which was normocytic and normochromic.[14] Diffuse bone marrow involvement is associated with suppression of haematopoiesis which manifests as thrombocytopenia, leukopenia or pancytopenia. Sometimes, leucoerythroblastic reaction is seen on PBS which is indicative of bone marrow fibrosis/ infiltration.[2,14] However, absence of leucoerythroblastic reaction does not necessarily mean absence of metastasis.[15] Only two of our cases showed metastasis. One of the aspirates was too dilute to opine. BMB is more sensitive than BMA and helps in the assessment of cellularity, fibrosis and confirmation of metastasis by immunohistochemistry (IHC).[16] Due to unavailability of BMB, we could not perform IHC and comment on cellularity was also not possible. This is one of the drawbacks of this study. BMA and BMB are complementary to each other. BMB is helpful especially when BMA is dilute or yields a dry tap. Also, we could have performed special stain like reticulin to grade the degree of fibrosis.[17,18] There have been studies where bilateral BMB were performed and there was significant increase in the yield of metastasis.[18,19] So, it is always better to have BMB along with BMA.CSF cytology which was done in four cases revealed no atypical cells. Patients suffering from cancer are usually referred to higher centres for chemotherapy. So, most of the patients from our hospital were transferred to special cancer institutes for further management which resulted in a small sample size.

CONCLUSION

We attempted a novel study of bone marrow involvement in non-haematological neoplasm like RB. Bone marrow examination is an important adjunct in the staging and management of RB. Confirmation of metastasis by IHC cannot be over emphasized and should be done in all cases if possible. Bone marrow and CSF involvement entails a dismal prognosis. With the advent of newer chemotherapy regimens, it is always better to plan BMA and bilateral BMB if possible especially for staging purposes and CSF examination in almost all cases so that the patients receive appropriate treatment and there is preservation of vision with maximum disease free survival.

Conflicts of Interest: There are no conflicts of interest.

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Ethical statement: No ethical issues publishing this article.

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