Teferi B, Taye B, Hailu SS, Raya K, Melkamu K. Bilateral Retinoblastoma with Lumbar Spine and Forearm Metastasis, Six Years after the Initial Presentation: A Rare Case Report. *East Cent Afr J Surg*. 2024;29(3):4-8. doi:10.4314/ecajs.v29i3.2

Case Report

Bilateral Retinoblastoma with Lumbar Spine and Forearm Metastasis, Six Years after the Initial Presentation: A Rare Case Report

Bezawit Teferi, MD[1][a], Bemnet Taye, MD[2], Samuel Sisay Hailu, MD[2], Kassahun Raya, MD[3], Kidest Melkamu, MD[3]

[1] Department of Orthopedic surgery, School of Medicine, College of Health Science, Addis Ababa University, [2] Department of Diagnostic Radiology, School of Medicine, College of Health Science, Addis Ababa University, [3] Department of Pathology, School of Medicine, College of Health Science, Addis Ababa University

Keywords: Retinoblastoma, Secondary Malignancy, Metastasis

https://doi.org/10.4314/ecajs.v29i3.2

East and Central African Journal of Surgery

Vol. 29, Issue 3, 2024

Abstract

Retinoblastoma is one of the most common childhood intraocular tumours. Extra-ocular extension is rare, but the risk of systemic metastasis increases with late diagnosis. We report a case of retinoblastoma metastasis to the forearm six years after the first diagnosis was made and treated. It is believed to add to our understanding of retinoblastoma metastasis, and this relatively uncommon disease course.

Introduction

Retinoblastoma is the most common childhood intraocular malignant tumor.[1,2] The majority of global case burden comes from low and middle-income countries associated with guarded outcomes.[3] Retinoblastoma can be heritable secondary to germ-line mutation of the RB1 gene. This pattern is common in the early years of life and is mostly unilateral, unlike a non-heritable form which appears later. Several studies revealed that retinoblastoma affects nearly 1 in 16,000 – 18,000 births, with an incidence of 7000 – 8000 new cases yearly. The incidence is three times higher in children under five than in those under three.[4] The mean age of diagnosis for retinoblastoma is around 1 year old for bilateral and 2 years for unilateral disease.[5] A nationwide study in Uganda revealed a 45% 3-year survival rate compared to 100 % in countries with no resource limitation.[6]

The incidence of retinoblastoma is around 2310 in East Africa second only to the West Africa region with 7824 incidences. There is a trend towards delayed presentation and diagnosis, treatment discontinuity by the family, and significant gap in multidisciplinary treatment resulting in increased risk of disease relapse, systemic metastasis and poorer prognosis with a mortality of 40-70 % in low income countries.[7] Clinical presentation of patients includes white ocular reflex, decreased vision, eye pain, and Glaucoma.[8] Microscopic histological examinations show small hyperchromatic cells with a high nuclear-to-cytoplasmic ratio with multifocal areas of necrosis and calcification. Tumor invasion of the surrounding structures appears as solid nests of cells infiltrating surrounding borders, and no necrosis.[9]

Patients with delayed diagnosis have a higher risk of developing metastatic disease, and studies have shown extraocular retinoblastoma occurring at a mean age of 33 and 38 months. Extrascleral extension of primary tumors is the most important risk factor for distant metastasis, due to access to the vascular and lymphatic system outside the eye.[5] Nearly all retinal recurrences appear within three years of the initial treatment and follow-up, with a 6-45% recurrence following all options of initial treatment.[10,11] It can also spread to the bones and lymph nodes and unlike all the other malignancies, rarely to the lungs.[4] Bilateral tumours are discovered and treated at a younger age than unilateral Retinoblastoma. Even if many studies have shown equal

a Corresponding author: bezawit.teferi@aau.edu.et

risk of metastasis in both groups, delay in diagnosis for unilateral cases might increase the risk.[12]

Case Report

Our patient is a six and half years old female child who came to our clinic with left forearm pain, and swelling of two months duration. Examination revealed a mildly tender, firm circumferential swelling over the distal third of the left forearm, her distal neurovascular status was normal and comparable to the right side (Figure 1). She has a surgically enucleated eye on the left side, with no other significant findings elicited. Imaging of the forearm revealed a permeative lesion over the whole length of the radius suggesting a possible presentation of osteosarcoma and she was subsequently admitted for open biopsy (Figure 2).

Her medical history begins with an initial presentation to an ophthalmology clinic with a complaint of bilateral eye leucorrhoea at 11 months of age. After a diagnosis of extensive intraocular retinoblastoma was made both eyes were surgically enucleated. The initial pathology report of the surgically removed eyes and tumour showed retinoblastoma with extension to the uveal tract, and no involvement of the optic nerve. Post-operatively 6 cycles of first-line chemotherapy regimen including Vincristin, Etoposide, and Carboplatin was given for its high-risk pathology. Subsequently, a follow-up MRI (Magnetic Resonance Imaging) showed no radiologic evidence of recurrence or residual enhancing tumor in the orbit, or signs of intracranial involvement (Fig 3).

At the age of 4 years and 3 months, she came back with a complaint of left eye swelling. A computed Tomography (CT) scan showed a left eye globe soft tissue mass suggestive of Retinoblastoma and was treated with External Beam radiotherapy for 3 weeks. A year into her follow up she came with an acute lower back pain radiating down to her thighs bilaterally, neck swelling, and difficulty walking. Neck and Abdominal Ultrasound showed bilateral cervical, mesenteric and para-aortic lymphadenopathy. Bone marrow biopsy was taken which demonstrated normal trilineage hematopoiesis, and Thoraco-Lumbar spinal MRI was suggestive of vertebral metastasis evidenced by L2 vertebral collapse (Fig 4). In light of the new diagnosis of vertebral and Lymph node metastasis, she was treated with high-dose intravenous dexamethasone, and 6 cycles of combination chemo-radio therapy including vincristine, doxorubicin, cyclophosphamid, and MESNA. The patient had no residual complications from the vertebral metastasis, and systemic studies didn't show involvement of other body parts.

After 14 months of the new development, she started developing left forearm pain, and swelling. During her initial admission, an incisional biopsy was done and histological sections were indicative of a round blue cell tumour likely retinoblastoma (Fig 5). Immunohistochemistry was done which revealed tumour cells expressing NSE and Synaptophysin. The study was negative for Vimentin, CK, CD99, BCL2, NKX2-2, and Desmin suggesting Retinoblastoma metastasis to be the cause of the forearm swelling. In due course, she was put on palliative Radiotherapy for painful

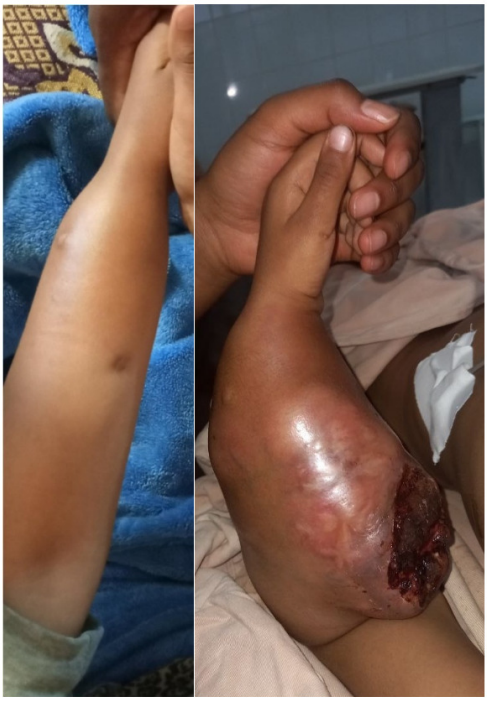

Fig 1. Initial (left side), and final (right side) pictures showing progress of forearm swelling

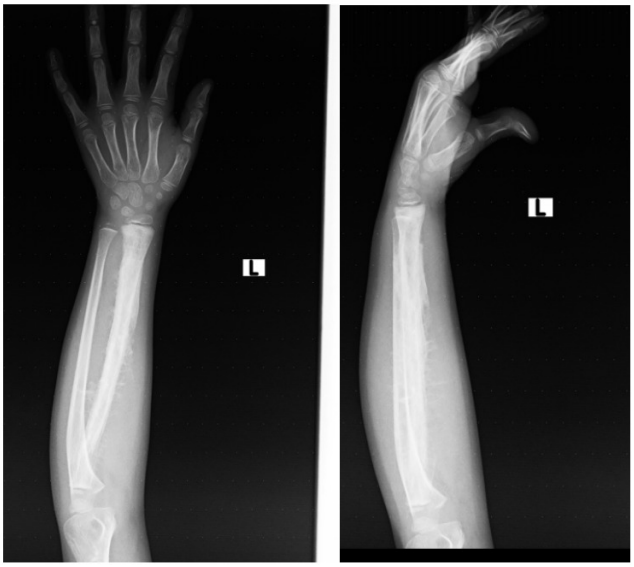

Fig 2. AP and Lateral Left Forearm Radiograph showing predominantly sclerotic permeative lesion with wide zone of transition involving the whole length of the left radius. There is associated lamellated, codman and hair on end type of aggressive periosteal reaction and associated mild soft tissue mass. The included ulna, carpal bones, metacarpals and phalanges are normal.

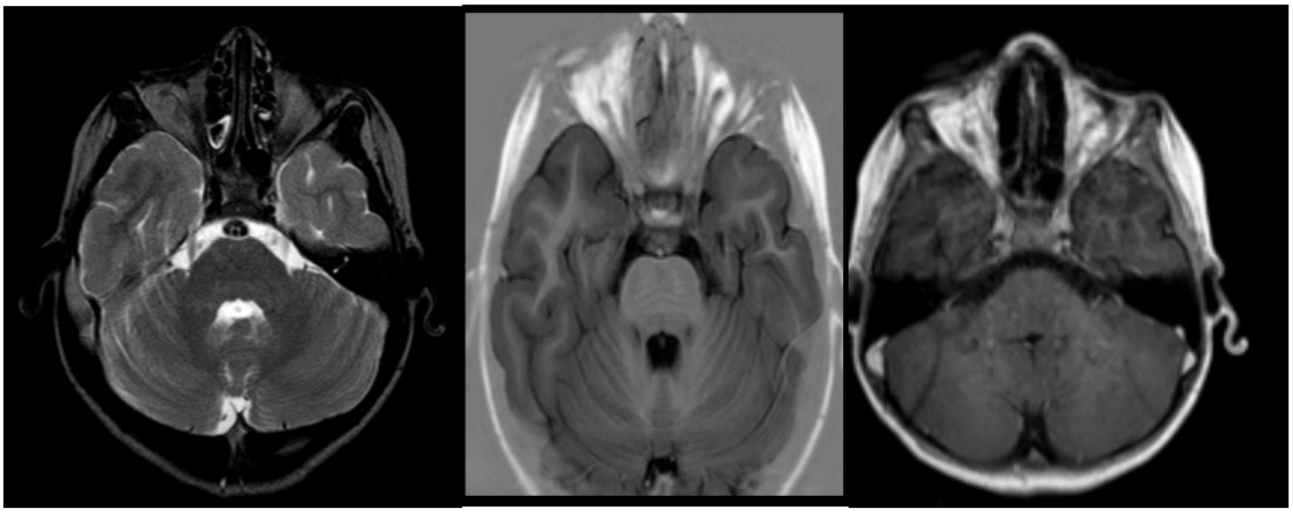

Fig 3. Axial T2W and T1W and T1 +C MR images demonstrate post surgical enucleation of the bilateral orbits with no enhancing lesion seen

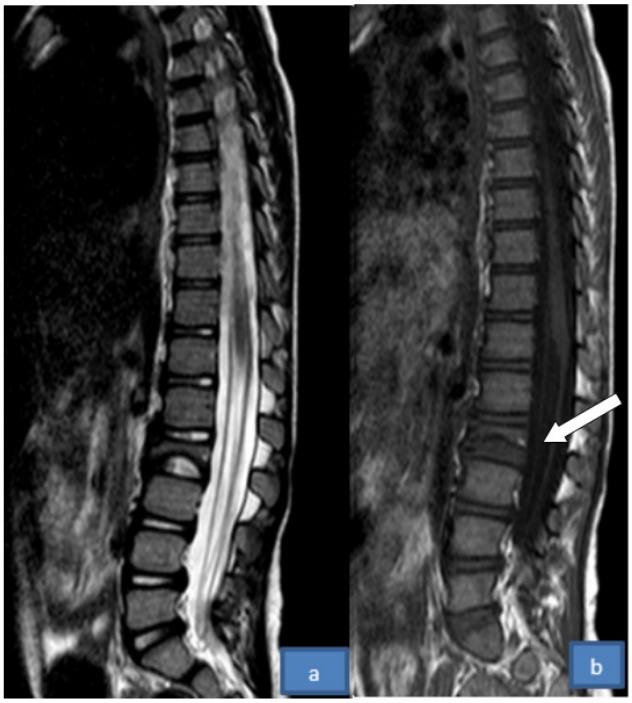

Fig 4. Sagital T2 (a) and T1 (b) lumbar MRI showing vertebral body height loss of L2 (white arrow)

bone metastasis followed by transhumeral amputation with clear microscopic margins.

Discussion

Local eye-preserving therapies such as radiotherapy have been shown to increase the risk for secondary cancers, commonly sarcomas in the field of radiation. Since 1996 systemic chemotherapy replaced radiotherapy due to its concern of inducing secondary cancers, especially if alkylating agents are used.[13] The most frequent site for distant metastases, through the systemic blood flow, is the bone marrow which may appear as primary bone tumours and needs to be carefully investigated.[14] Both Focal and diffuse involvement of bones and bone marrow can occur, most commonly within two years of diagnosis as metastases in later years are extremely rare. Retinoblastoma patients are known to have an increased risk of secondary malignant neoplasms (SMN) like osteosarcoma, leiomyosarcoma, spindle cell sarcoma, malignant fibrous histiocytoma, rhabdomyosarcoma, angiosarcoma, Ewing sarcoma, and PNET (Primitive neuro-ectodermal tumours), typically occurring after 8–15 years of latency. Thorough investigations using histological, immunologic, and imaging is required to distinguish between these two entities. The Involvement of multiple bones supports the diagnosis of metastases than multifocal SMN.[14,15]

Metastatic retinoblastoma outside the Central Nervous System is rare and diagnosis is hard due to similar histologic appearance with other bone tumours.[16] Metastases to extremities appear radiologicaly as permeative bone destruction and periosteal reaction with a tendency to be bilateral.[17] Histologically they present as small round or polygonal cells with hyperchromatic nuclei and scanty cytoplasm. They typically form rosettes where tumour cells surround a central basement membrane called Flexner-Wintersteiner rosettes. Both local and distance metastasis with intracranial extension including treatment-induced secondary tumors are known to be poor prognostic characteristics.[18] Metastatic retinoblastoma has been rarely curable, a reason for the poor prognosis associated with metastasis. This is changing recently with the advent of a multimodal treatment including multi-agent chemotherapy, and radiotherapy with autologous stem cell transplantation followed by high-dose chemotherapy to consolidate the response, as seen from different case series.[19]

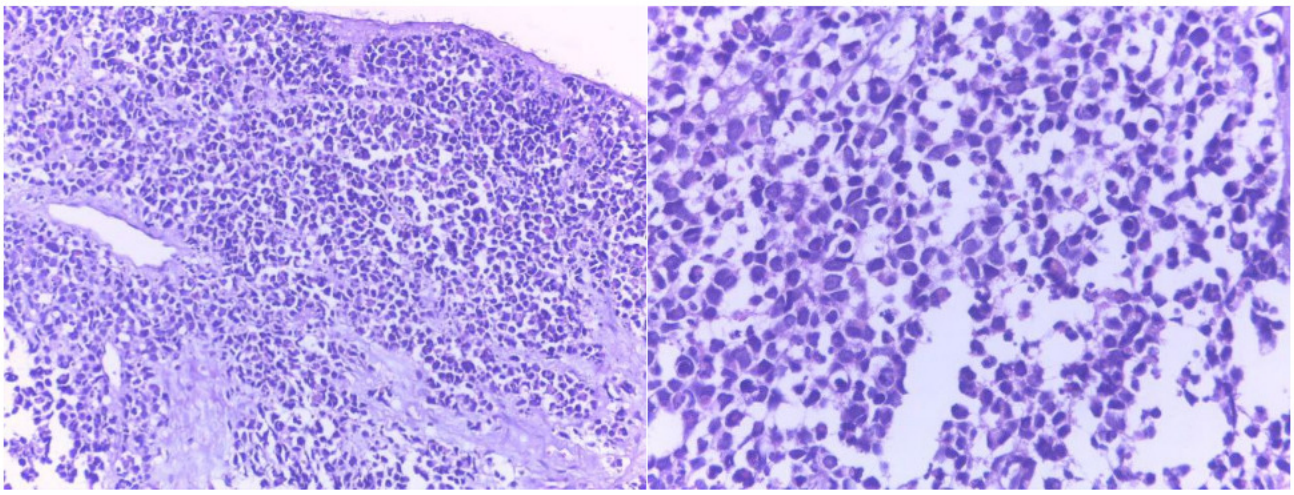

Fig 5. Sections showing nests and sheets of moderately pleomorphic round blue cells with infiltration of the bony trabecular spaces, features suggest round blue cell tumor.

Studies have shown initial diagnosis before two years of age and subretinal seeds at diagnosis to be predictive of recurrence.[11] It is evident that our patient's age during her initial presentation has increased her risk of recurrence and the authors believe there might be a possibility of missed sub-retinal seeding initially. Due to her initial treatment with radiotherapy and alkylating agents, she is also believed to have an equal risk for developing secondary tumors including osteosarcoma, which is an important differential. As seen in this case having access to advanced histological investigations including immune histo-chemistry studies is critical in differentiating between the possible causes in such presentation. Repeated exposure to radiation including from an Initial treatment with external beam radiotherapy, and repeated radiologic investigations is related to an increased risk of recurrence especially in children with hereditary retinoblastoma. Thus new recommendations include minimizing repeated exposure to imaging modalities, opting for MRI as an initial evaluation tool instead of a CT scan, and utilizing alternative conservative measures is in place.[20]

Even if new and advanced treatment regimens are not readily available in this setting we believe local control of the disease process and post-surgical chemotherapy will give patients the best possible outcome. We have also observed delays in reaching a definitive diagnosis, and the lack of a multi-disciplinary approach to treat such patients has a direct impact on the prognosis of our patients. In addition, evidences suggests lifelong follow-up of children treated for retinoblastoma is warranted to help children with societal integration, follow-up of late recurrences, and parental counseling for genetic testing.[21] Physicians in resource-limited settings are encouraged to advocate for the establishment of early detection facilities, and lifelong follow-up plans for patients with retinoblastoma.

CONCLUSION

In conclusion it is important to consider recurrence of retinoblastoma in patient with new onset swelling in unusual sites even after years of their initial presentation. It is also important to have lifelong follow up for children with retinoblastoma in order to timely diagnose and treat patients.

Acknowledgement

We would like to thank the parents of the child for allowing us to study the case.

Financial Support and Sponsorship

None.

Conflict of Interest

The authors have no conflict of interest to reveal.

Submitted: December 01, 2022 EAT, Accepted: August 25, 2024 EAT

References

1. Wong JR, Tucker MA, Kleinerman RA, Devesa SS. Retinoblastoma Incidence Patterns in the US Surveillance, Epidemiology, and End Result Program. *JAMAOphthalmol*. 2014;132(4):478-483. doi:10.1001/jamaophthalmol.2013.8001

2. Young JL, Smith MA, Roffers SD, Liff JM, Bunin GR. Retinoblastoma. In: Reis LAG, Smith MA, Gurney JG, eds. *Cancer Incidence and Survival Among Children and Adolescents: United States SEER Program 1975–1995*. National Institutes of Health; 1999.

3. Finger PT, Tomar AS. Retinoblastoma outcomes: a global perspective. Published online January 27, 2022. doi:10.1016/S2214-109X(2100598-2)

4. Houston SK, Murray TG, Wolfe SQ, Fernandes CE. Current update on retinoblastoma. *Int Ophthalmol Clin*. 2011;51(1):77-91. doi:10.1097/IIO.0b013e3182010f29

5. Gündüz K, Müftüoglu O, Günalp I, Unal E, Taçyildiz N. Metastatic retinoblastoma clinical features, treatment, and prognosis. *Ophthalmology*. 2006;113(9):1558-1566. doi:10.1016/j.ophtha.2006.03.039

6. Waddell K, Matua M, Bidwell C, et al. A ten-year study of Retinoblastoma in Uganda: An approach to improving outcome with limited resources. *Cancer Epidemiology*. 2021;71:101777. doi:10.1016/j.canep.2020.101777

7. Sherief ST et al. Health Services Needs Assessment for Retinoblastoma in Ethiopia. *JCO Glob Oncol*. 2023;9:e2200445. doi:10.1200/GO.22.00445

8. O'Brien JM. Retinoblastoma: Clinical Presentation and the Role of Neuroimaging. *AJNR Am J Neuroradiol*. 2001;22(3):427-429.

9. Singh L, Kashyap S. Update on pathology of retinoblastoma. *Int J Ophthalmol*. 2018;11(12):2011-2016. doi:10.18240/ijo.2018.12.22

10. Shields CL, Honavar SG, Shields JA, Demirci H, Meadows AT, Naduvilath TJ. Factors Predictive of Recurrence of Retinal Tumors, Vitreous Seeds, and Subretinal Seeds Following Chemoreduction for Retinoblastoma. *Arch Ophthalmol*. 2002;120(4):460-464. doi:10.1001/archopht.120.4.460

11. Berry JL, Kogachi K, Murphree AL, Jubran R, Kim JW. A Review of Recurrent Retinoblastoma: Children's Hospital Los Angeles Classification and Treatment Guidelines. *Int Ophthalmol Clin*. 2019;59(2):65-75. doi:10.1097/IIO.0000000000000269

12. Finger PT, Harbour JW, Karcioglu ZA. Risk factors for metastasis in retinoblastoma. *SurvOphthalmol*. 2002;47(1):1-16. doi:10.1016/s0039-6257(01)00279-x

13. Temming P, Arendt M, Viehmann A, et al. Incidence of second cancers after radiotherapy and systemic chemotherapy in heritable retinoblastoma survivors: A report from the German reference center. *Pediatr Blood Cancer*. Published online 2017. doi:10.1002/pbc.26193

14. Ting SC, Kiefer T, Ehlert K, et al. Bone metastasis of retinoblastoma five years after primary treatment. *Am J Ophthalmol Case Rep*. 2020;19:100834. doi:10.1016/j.ajoc.2020.100834

15. Kuruva M, Mittal BR, Kashyap R, Bhattacharya A, Marwaha RK. Bilateral retinoblastoma presenting as metastases to forearm bones four years after the initial treatment. *Indian J Nucl Med*. 2011;26(2):115-116. doi:10.4103/0972-3919.90268

16. Meredith DM, Charville GW, Fletcher CDM, Hornick JL. Distantly Metastatic Retinoblastoma to Soft Tissue and Bone: A Challenging Diagnosis Highlighting the Utility of CRX. *Am J Surg Pathol*. 2021;45(6):820-824. doi:10.1097/PAS.0000000000001620

17. Reed MH, Culham JA. Skeletal metastases from retinoblastoma. *J Can Assoc Radiol*. 1975;26(4):249-254.

18. Castelino-Prabhu S, Stoll LM, Li QK. Metastatic retinoblastoma presenting as a left shoulder soft tissue mass: FNA findings and review of the literature. *DiagnCytopathol*. 2010;38(6):440-446. doi:10.1002/dc.21252

19. Rodriguez-Galindo C, Wilson MW, Haik BG, et al. Treatment of metastatic retinoblastoma. *Ophthalmology*. 2003;110(6):1237-1240. doi:10.1016/S0161-6420(03)00258-6

20. de Graaf P, Göricke S, Rodjan F, et al. Guidelines for imaging retinoblastoma: imaging principles and MRI standardization. *Pediatr Radiol*. 2012;42(1):2-14. doi:10.1007/s00247-011-2201-5

21. Seth R, Singh A, Guru V, Chawla B, Pathy S, Sapra S. Long-term follow-up of retinoblastoma survivors: Experience from India. *South Asian J Cancer*. 2017;6(4):176-179. doi:10.4103/sajc.sajc_179_16