Retinoblastoma Metastatic to Bone: Case Series and Literature Review

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AUTHOR'S CONTRIBUTIONS

All authors contributed equally to this work and were responsible for the study concept and design. All authors drafted the manuscript, contributed to the article, and approved the final manuscript.

DISCLOSURES

The authors declare no conflicts of interest.

CONSENT

No.

HUMAN AND ANIMAL RIGHTS

The report adhered to the tenets of the Declaration of Helsinki and was HIPAA compliant.

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ABSTRACT

Retinoblastoma (RB) is a treatable tumor that arises in the retina, mainly affecting children under 2 years old. It results from a mutation on the long arm of chromosome 13, specifically of the RB1 gene (13q14). Patients with the hereditary form of RB have a higher incidence of metastases and secondary cancer development. These cancers, including metastasis, secondary malignant neoplasms, and radiation-associated sarcomas, are rare and typically occur in advanced stages. Although the overall prognosis for RB is generally favorable, it declines significantly when metastases develop. While rare, the most common sites of RB metastasis are the brain, osseous structures, cervical nodes, central nervous system, lungs, and liver. Here, we present the clinical and radiologic features of three patients with osseous metastasis from RB and review current literature, including the development of secondary malignant neoplasms, radiation-associated sarcomas, prognosis, and treatment options.

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CASE REPORT

BACKGROUND

Osseous metastases from retinoblastoma (RB) are extremely rare, may occur months to years after diagnosis, and are associated with a poor prognosis [1]. Management is further complicated by these patients' increased risk of secondary malignant neoplasms (SMNs) and radiation-associated sarcomas [1-7]. Understanding the clinical signs and imaging features of metastatic RB, SMNs, and radiation-associated sarcomas is essential for radiologists and clinicians managing patients with RB to ensure accurate diagnosis and appropriate management.

CASE DESCRIPTIONS

Case 1: A 1-year-old male was diagnosed with RB in the right eye, and genetic testing identified a translocation between chromosomes 4 and 13. Intravenous chemotherapy consisting of carboplatin, iodamide, and etoposide with adjuvant radiation did not reduce the tumor size; thus, an enucleation was performed. Approximately 5 years later, he experienced pain in his lower right extremity after a fall. Over the following month, a progressively enlarging soft tissue mass developed at the site in the painful lower extremity. Plain radiographs showed a segmental lesion of the fibular diaphysis with permeative bone destruction, periosteal reaction, and a soft tissue mass (Figure 1A). A nuclear medicine bone scan showed increased uptake in the proximal right fibular diaphysis (Figure 1B), and a PET/CT showed no other sites of disease (not shown). An MRI demonstrated an expansile lesion involving the proximal right fibula (Figure 1C). Subsequent biopsy revealed metastatic RB. He underwent surgical resection of the affected fibula (Figure

1D) and IV chemotherapy consisting of ifosfamide, carboplatin, and etoposide, alternating with vincristine, Adriamycin, and cyclophosphamide. The patient was followed at our institution for approximately 3 years without recurrence and then was lost to follow-up, possibly because he resides in another country.

Case 2: A 14-month-old female patient presented with right periorbital swelling with mild erythema, right conjunctival injection, and decreased vision in the right eye. An MRI showed a right intraocular mass (Figure 2A), leading to the diagnosis of RB. The patient underwent enucleation of the right eye. Genetic testing identified two RB mutations in the tumor, while germline testing was negative. Approximately one year later, she presented to the emergency department with swelling over her forehead. A CT scan revealed permeative lesions in the calvarium and the left sphenoid bone, along with a soft-tissue mass lateral to the left orbit (not shown). An MRI subsequently revealed metastatic lesions in the left frontal calvarium with epidural extension, as well as involvement of the bilateral sphenoid wings, orbits, mandible, and cervical lymph nodes (Figures 2B-2E). The day after the MRI, a lumbar puncture was performed, and the results were consistent with metastatic RB. Further evaluation revealed liver metastases (Figure 2F). The patient received IV chemotherapy consisting of carboplatin, thiotepa, and etoposide, and autologous stem cell transplants, with resolution of the metastatic disease. Subsequent imaging over 3 years has revealed no recurrence.

Case 3: A 6-week-old male was diagnosed with bilateral RB. He was treated with 6 cycles of IV vincristine, carboplatin, and etoposide, accompanied by adjuvant laser and cryotherapy, and showed a positive response. When a relapse occurred in the vitreous of the right eye 1 month later, it was treated with enucleation, while a recurrence in the left eye was managed with laser, cryotherapy, and retinopexy. He remained disease-free for about 15 years until he developed non-traumatic pain in the right knee and distal thigh. Despite treatment with anti-inflammatory medication, the pain persisted. Plain radiographs revealed an aggressive, ill-defined, permeative lesion in the distal femoral diaphysis and metaphysis with abnormal periosteal reaction (not shown). An MRI showed a lesion in the femoral shaft, and a PET/CT showed no other sites of disease (not shown). A subsequent biopsy was interpreted as metastatic RB, and he was treated with IV thiotepa, etoposide, and carboplatin followed by autologous stem cell rescue and proton therapy (36 Gy). About 6 years after treatment of the femoral metastasis, he developed intermittent pain in the right upper thigh. Imaging revealed a lytic intracortical lesion in the posterior cortex of the right femoral shaft within the radiation field (Figures 3A-3C). A percutaneous biopsy of the lesion identified a radiation-associated high-grade osteosarcoma. The patient then underwent radical resection of the right femoral diaphysis and an intercalated allograft with lateral stabilization using a long compression plate (Figure 3D). He also received adjuvant IV cisplatin, doxorubicin, and methotrexate, and a PET/CT examination 4 months later revealed no evidence of recurrent or metastatic disease.

DISCUSSION

Etiology

We describe three children with RB who developed bony metastasis at various stages of treatment and follow-up after the initial diagnosis of the primary ocular tumor. The onset of bony metastasis occurred within one year of treatment of the ocular tumor in one case, but in the other two cases, it occurred during the long-term follow-up period at 5 and 15 years, respectively, highlighting the importance of long-term follow-up and surveillance for metastasis in patients with RB.

In children, the most frequently diagnosed primary intraocular tumor is RB. It is diagnosed in approximately 8,000 to 10,000 children each year and shows no gender, racial, or geographic predilection [8]. RB develops when the long arm of chromosome 13 (13q14) harbors a mutation in the RB1 tumor suppressor gene [9]. Loss of one RB1 allele predisposes the patient to cancer, and loss of the other allele initiates the development of RB [8]. Heritable RB is transmitted in an autosomal dominant manner with high penetrance (>90%) but marked variability. However, most cases result from a de novo pathogenic RB1 variant [9].

Unilateral RB, diagnosed in 60% of cases, usually occurs around 2 years old and is generally not hereditary. By contrast, bilateral RB tends to be hereditary, linked to genetic cancer predisposition syndromes, and usually occurs at the age of 1 year [4]. Approximately 80% of hereditary cases are diagnosed before age 4 [10].

A metastasis develops in approximately 4.8% to 5.8% of RB cases [1]. Half of these metastases occur within the intracranial region through several routes, including direct invasion via the optic nerve, hematogenous spread, or through lymphatic channels [5, 6, 7]. Bony metastasis is the second most common site for RB metastasis, with the ribs and vertebrae most frequently affected due to high hematopoietic activity, especially in children [11-13]. Other sites of metastasis include cervical nodes, lungs, and liver [1,14]. Distant metastases are uncommon, typically occurring only in advanced stages of the disease [1].

Differential Diagnosis

In addition to the risk of metastasis, survivors of RB, especially those with the hereditary form, face an increased risk of developing SMNs. Common SMNs include bone and soft-tissue sarcomas (such as osteosarcoma and fibrosarcoma) and melanomas. Brain tumors, skin cancers, breast cancer, endocrine cancers, gastrointestinal and genitourinary cancers occur at higher rates than in the general population [2,3]. The incidence of new cancer 50 years after diagnosis differs markedly between hereditary and non-hereditary RB at 36% and 5.7%, respectively [15]. The incidence of SMNs after RB

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increases with the length of time from initial diagnosis, reaching a cumulative incidence of 10% at 10 years after diagnosis [16].

Radiation therapy and alkylating chemotherapeutic agents used to treat RB can increase the risk of radiation-associated sarcomas [1,4-7]. Criteria for classifying a tumor as radiation-associated include its development within the boundaries of a previously irradiated region, a histology different from that of the original tumor, and an asymptomatic latent period of more than 4 years [17]. One of the most common radiation-associated tumors is osteosarcoma, as the RB1 mutation has been linked to its development [18]. Patient #3 in our series developed a radiation-associated osteosarcoma approximately 6 years after receiving radiation at the site of a femoral metastasis.

Symptoms

The two most common signs of RB, leukocoria (white reflection in the pupil) and strabismus (misalignment of the eyes), are usually identified through a fundus examination [4]. In advanced stages, patients may exhibit changes in iris color, corneal and globe enlargement, signs of inflammation, and exophthalmos [10]. Symptoms of metastatic RB vary depending on where the disease has spread and can include decreased appetite, headaches, weight loss, bone and joint pain, and lumps under the skin, especially in the neck [19, 20].

Diagnosis and Imaging

RB is diagnosed via leukocoria noted by a pediatrician or via ophthalmologic examination. After initial diagnosis, neuroimaging helps confirm RB extension and staging [21,22]. Neuroimaging includes high-resolution T2-weighted and T1 post-contrast MRI. Small intraocular RBs within the retinal layers are best detected on heavily T2-weighted images, including FIESTA/3D CISS [10]. Evaluation should localize RB within the globe and exclude both extraocular extension and optic nerve invasion. It is also important to assess the iris, anterior chamber, and ciliary body [23,24]. Subretinal tumor seeding, defined as RB that proliferates between the retina and the choroid, can also occur. Choroidal invasion is accompanied by choroidal thickening, with or without enhancement, or by choroidal thinning with decreased enhancement [25-27].

RB can extend through the sclera into an extraocular location within the retrobulbar fat, or spread to the dural sheath and optic nerve, and then to the intracranial space. RB may also metastasize via lymphatic or hematogenous routes [6, 7]. Examining the sella and suprasellar regions and the pineal gland region is important on initial MRIs to exclude the development of trilateral or quadrilateral RB. Post-treatment imaging focuses on surveillance to detect CSF seeding, trilateral or quadrilateral RB, and local or intracranial recurrence, and distant metastases [14,28].

Prognosis

RB has an excellent prognosis, with a cure rate exceeding 99% [29]. However, when RB metastasizes, it portends a poor prognosis [19], with a survival rate as low as 28.7% [29,30]. With aggressive treatment, 2 of the 3 patients in our study with osseous metastasis have been disease-free for 3 years, with 1 lost to follow-up. The final patient developed

a radiation-associated sarcoma about 6 years after treatment for a femoral metastasis and is currently disease-free 4 months after treatment.

Treatment

RB treatment is based on the extent and laterality, International Classification of Retinoblastoma staging, genetic testing, psychosocial considerations, and available resources. Current treatment options include IV chemotherapy, intra-arterial chemotherapy, intravitreal chemotherapy, periocular chemotherapy, cryotherapy, transpupillary thermotherapy, radiation therapy, and enucleation [30-32].

While these treatments are typically effective, the prognosis for patients with metastatic RB treated with traditional chemotherapy and radiation is usually poor [33]. Therefore, a more multidisciplinary approach is necessary. Comprehensive treatment methods may offer effective options for patients with metastatic disease [30]. SMNs should be distinguished from metastatic RB and radiation-associated tumors, as treatment strategies differ, and histological confirmation is essential [34].

CONCLUSION

The three cases in our report underscore the importance and complexity of diagnosing, treating, and monitoring patients with RB. Not only can RB spread directly to the brain and metastasize to distant sites, including osseous structures, but SMNs can also occur in these patients. Further complicating management is the development of radiation-associated tumors after treatment. Radiologists and other physicians managing patients with RB should be aware of the complex nature of this disease to avoid delays in diagnosis and treatment. Furthermore, because bony metastasis may develop years after initial treatment, long-term surveillance is recommended.

TEACHING POINT

Metastases to the bones from RB are extremely rare. Osseous metastases may appear years after treatment and can include symptoms such as pain, swelling, hypercalcemia, and fractures. Understanding the clinical signs and imaging features of metastatic RB is essential for accurate diagnosis and proper management. Long-term follow-up and monitoring for metastasis are also crucial, as metastasis can occur years later and is often associated with a poor prognosis.

QUESTIONS

Question 1: Which of the following can be used to detect calcification when imaging the retina?

A: Ultrasound

B: MRI

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C: CT
D: High-resolution gradient echo T2-weighted sequence
E: All of the above

Correct answer E

Explanation: All three of these imaging methods can be used to identify calcification when imaging the eye. Due to technical advances, the MRI and CT are almost as accurate as US. High-resolution heavily T2-weighted sequences have shown promising results in detecting calcification [10].

Question 2: Associated image findings with metastatic retinoblastoma to long bones include which of the following?

A: Lytic intracortical lesion
B: Intramedullary lesion
C: Enhancing lesion on MRI
D: Uptake on bone scan
E: All of the above

Correct answer: E

Explanation: All of these are associated with image findings of metastatic retinoblastoma.

Question 3: Which of the following statements is true?
A: Retinoblastoma is the fifth most common pediatric sarcoma
B: Metastatic retinoblastoma has a better prognosis than nonmetastatic retinoblastoma
C: The most common site of metastasis among cases of metastatic retinoblastoma is the intracranial region
D: Nonhereditary retinoblastoma has a higher incidence rate of second primary neoplasms
E: The cure rate for non-metastatic retinoblastoma in developed countries is 75%

Correct Answer: C

Explanation: Metastatic retinoblastoma can spread to the intracranial compartment via the optic nerve [5].

Question 4: Specific symptoms of retinoblastoma metastasis to the bone typically include all of the following except?

A: Joint pain
B: Limb pain
C: Hypercalcemia
D: Fractures
E: Seizures

Correct answer: E

Explanation: Specific symptoms of bone metastasis include fractures, hypercalcemia, joint and limb pain, while seizures is not.

Question 5: The differential diagnosis for metastatic retinoblastoma includes which of the following?
A: Secondary malignant neoplasms
B: Radiation-associated sarcomas
C: Benign bone cyst
D: Both A and B
E: None of the above

Correct answer: D

Explanation: Secondary malignant neoplasms and if a new lesion arises in a radiation field from prior treatment, then radiation-associated sarcomas would be the differential diagnosis of metastatic retinoblastoma.

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FIGURES

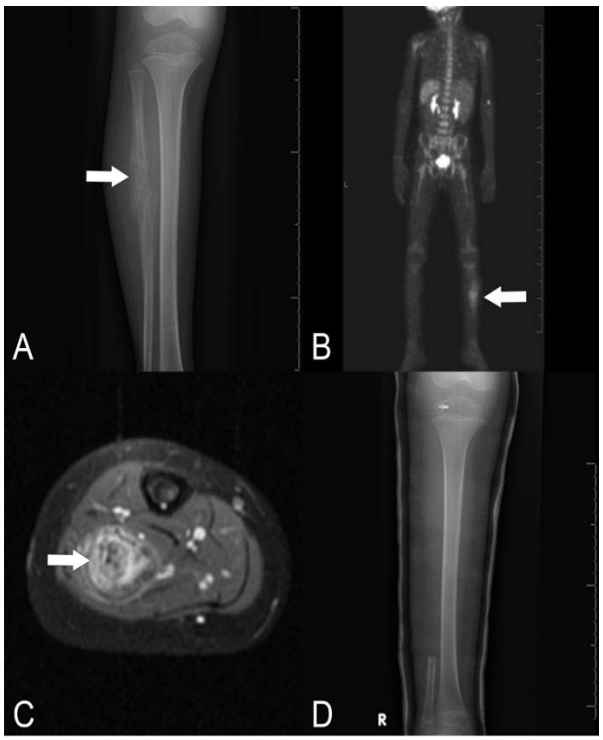

Figure 1: A 6-year-old male with metastatic RB to the right fibula. (A) Plain radiograph of the right lower extremity shows a segmental lesion of the tibial diaphysis with permeative bone destruction, periosteal reaction, and a soft tissue mass (arrow). (B) Nuclear medicine bone scan shows increased uptake in the proximal right tibial diaphysis (arrow). (C) MRI of the lower extremity with contrast shows a heterogeneously enhancing, expansile lesion involving the proximal right fibula (arrow). (D) Plain radiograph of the lower right extremity following tibial resection.

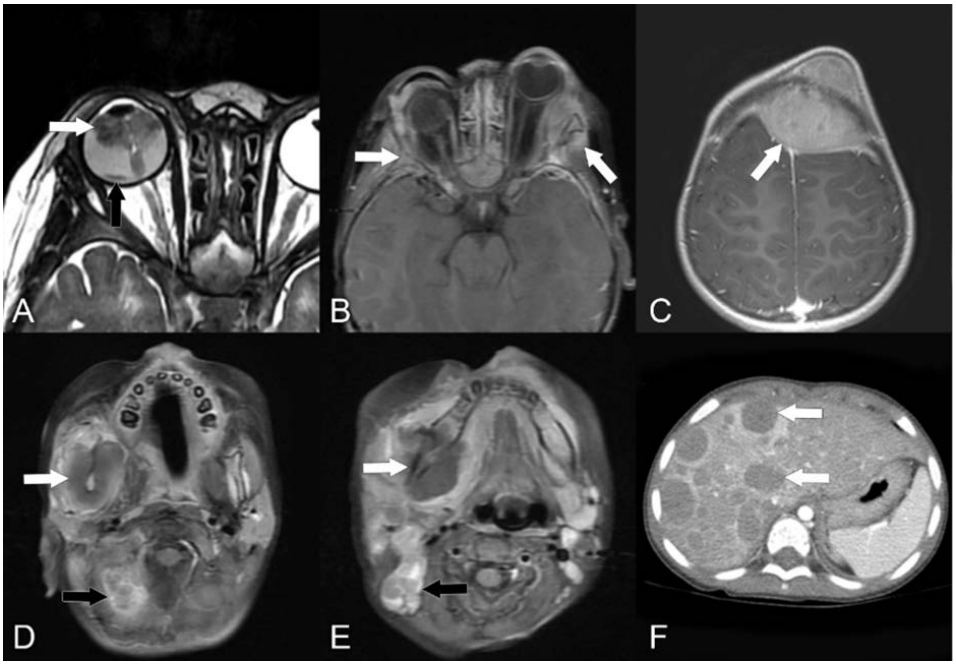

Figure 2: A 2-year-old male with metastatic RB to the calvarium, maxillofacial region, neck nodes, and liver. (A) Axial T2 MRI shows a hypointense mass in the vitreous of the right globe (white arrow) and a hypointense mass involving the right retina (black arrow). (B) Axial T1 post-contrast MRI shows metastases to the sphenoid bones bilaterally (arrows) with extension into the left greater than right orbit and proptosis of the left globe. (C) Axial T1 post-contrast MRI shows a left frontal calvarial metastasis with epidural extension and mass effect upon the frontal lobes (arrow). (D) Axial T1 post-contrast MRI shows a right mandible metastasis (white arrow) and a metastasis to the right occipital bone (black arrow). (E) Axial T1 post-contrast MRI shows a right mandible metastasis (white arrow) and a metastatic right upper neck node (black arrow). (F) CT abdomen with contrast shows multiple liver metastases (arrows).

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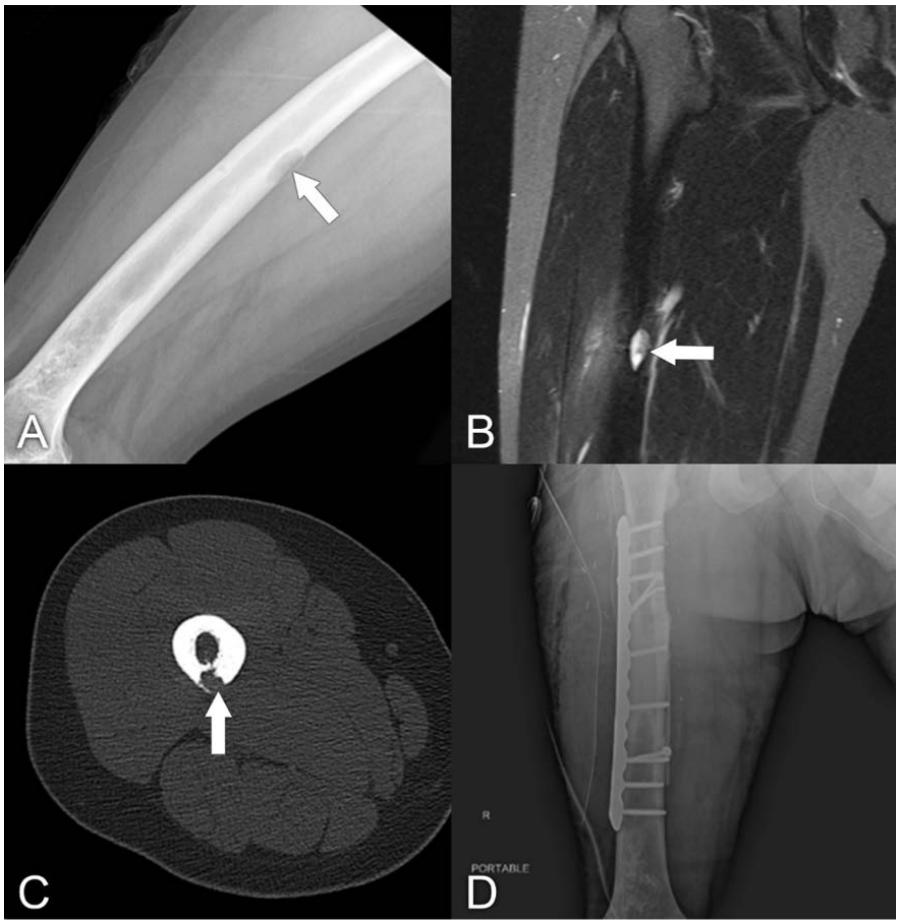

Figure 3: A 21-year-old male with metastatic retinoblastoma to the right femur who developed a radiation-associated osteosarcoma. **(A)** Plain radiograph shows a lytic lesion in the cortex of the right femoral diaphysis (arrow). (B) Coronal T1 post-contrast MRI shows an enhancing lesion in the cortex of the right femoral diaphysis (arrow). (C) Axial CT shows a lytic lesion in the cortex of the right femoral diaphysis (arrow). (D) Plain radiograph shows the right femur following tumor resection with repair using intercalated allograft and lateral stabilization with a long compression plate.

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KEYWORDS

Retinoblastoma, metastasis, bone, computed tomography, magnetic resonance imaging

ABBREVIATIONS

RB = Retinoblastoma
SMNs = Neoplasms

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