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CLINICAL CASE

Primary alveolar rhabdomyosarcoma of bone

Rabdomiosarcoma alveolar primario de hueso

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What do we know about the subject matter of this study?

Rhabdomyosarcoma is the most frequent soft tissue tumor in childhood. This entity should be considered in the differential diagnosis of small round blue cell bone tumors.

What does this study contribute to what is already known?

We describe this tumor in a rare location and discuss its clinical course and treatment. The diagnostic importance of imaging, histologic and genetic studies to achieve a diagnosis of certainty is emphasized in addition to the importance of protocolized and multimodal treatment.

Abstract

Rhabdomyosarcoma (RMS) is a malignant solid tumor of mesenchymal origin. It is the most common soft-tissue sarcoma in childhood and adolescence. 65% of cases are diagnosed before the age of 6. Histological subtypes include embryonal, alveolar, pleomorphic, and fused-cell RMS. The embryonal subtype is more frequent in children, while the alveolar one is more frequent in adolescents and adults. **Objective:** To describe the clinical presentation of primary alveolar rhabdomyosarcoma in a schoolgirl. **Clinical Case:** 7-year-old schoolgirl with one-month history of progressive pain in her left thigh. X-ray shows a lytic lesion in the left femur diaphysis. A study was performed with 2 biopsies, immunohistochemistry, and PAX-FOXO1 studies which were compatible with alveolar RMS. **Conclusion:** Primary alveolar rhabdomyosarcoma of the bone is rare, but it should be considered within the differential diagnosis of primary small-round-blue cell bone tumors. Despite presenting a poor prognosis cytogenetic, this type of tumor seems to have better biological behavior, which for a successful treatment makes necessary to have a high index of suspicion in order to install a multimodal therapy in the context of a national protocol.

Keywords:
Bone Tumor;
Alveolar Rhabdomyosarcoma of the Bone;
FOXO-1;
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Introduction

Rhabdomyosarcoma (RMS) is a malignant solid tumor that originates in mesenchymal cells involved in the development of striated muscle tissue. It is the most frequent soft tissue tumor in childhood, with an annual incidence of 4.5 new cases per 1,000,000 people under 15 years of age, 250 to 300 cases in the United States, and 15 to 20 cases in Chile[1,2]. It can be associated with familial syndromes such as Neurofibromatosis, Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome, or Costello syndrome[3]. Histologically, the tumor cells resemble those of skeletal muscle. It is classified according to histopathological findings into embryonal, alveolar, pleomorphic, and spindle cell subtypes[4,5].

Embryonal RMS is the most frequent and is associated with a better prognosis, with 82% survival at 5 years, while alveolar RMS is clinically more aggressive due to its propensity to present metastasis and recurrences, with 65% survival at 5 years[6]. This subtype shows characteristic genetic alterations, such as the t(2;13)(q35;q14) or the t(1;13) (p36;q14) translocation involving the FOXO1 and PAX3 or PAX7 genes. These genes lead to the production of new fusion proteins that act as transcription factors and inhibitors of myogenic differentiation, with oncogenic effects[7,8], which correlates with clinical evolution. This group of alveolar RMS expressing these fusion genes has a more aggressive behavior and worse prognosis[9].

Patients with embryonal and/or alveolar RMS even with FOXO-1 positive and localized disease, classified as low risk, have a survival rate of over 80% with multimodal treatment including chemotherapy, surgery, and/or radiotherapy depending on whether there was complete resection or control of the primary disease. On the other hand, patients with metastatic or recurrent disease have a 20-30% chance of resolution[10,11].

The most frequent location of RMS is head, neck, and male and female genitourinary, as well as trunk and limbs. Primary bone RMS, either embryonal or alveolar, is very rare and its clinical course is not completely defined. Its pathogenesis is not clear and the origin of the tumor cells is not from differentiated skeletal muscle cells but rather from pluripotent and mesenchymal stem cells with skeletal muscle differentiation[12].

The objective of this article is to describe the clinical presentation of a primary alveolar rhabdomyosarcoma of the bone in a schoolgirl.

Clinical Case

A 7-year-old female schoolchild, with no remarkable morbid history, with a 1-month history of progressive pain in the left thigh and claudication of this limb. She had no general condition involvement or other symptomatology.

Radiography of the left lower limb was performed, which showed a lytic lesion located in the femur diaphysis, with poorly defined borders, areas of cortical interruption, and periosteal reaction in an "onion-skin" pattern. The study was completed with MRI which showed a lytic tumor lesion with areas of central necrosis and low-signal-intensity concentric circular areas in the cortical zone. There was no soft tissue involvement. A bone scan was performed showing only an irregular uptake at the left femoral level, from the intertrochanteric region to the inferior metaphysis (figure 1).

Due to the clinical and imaging characteristics, Ewing's sarcoma or osteosarcoma was suspected, so the study was completed with a biopsy. Hematoxylin-Eosin staining showed small round blue cells, with positive immunohistochemistry for vimentin, desmin, and myogenin (figure 2), compatible with RMS. Given the infrequency of this diagnosis in a bone tumor, it was decided to repeat the biopsy for confirmation and also to perform a complimentary genetic study. A FISH test was performed which was positive for the FOXO-1 gene (Saint Jude Hospital, USA), which is consistent with alveolar RMS. Subsequently, tumor staging was performed with a chest CT scan and myelography, which were normal.

She started chemotherapy according to the national protocol for localized RMS, with Vincristine-Actinomycin-Cyclophosphamide. The treatment was well tolerated. The evaluation at week 12 of treatment showed a better defined femoral lytic lesion, without manifestations of disease in other areas. E*n-bloc*, free-margin resection of the tumor lesion was performed, with bone graft placement. The operative specimen showed 50% of necrosis.

The patient evolved favorably and continued with chemotherapy until completing the protocol at week 46. The end of treatment evaluation showed the disease in remission.

Currently, 5 years after diagnosis, the patient is in good condition, presenting only mild claudication secondary to mild shortening of the left lower limb. According to the usual criteria, the patient is considered cured of her underlying disease. However, she will be monitored periodically to evaluate the appearance of sequelae or long-term effects of chemotherapy.

Discussion

RMS is the most frequent solid soft tissue tumor in childhood. Morphologically, it is part of the so-called

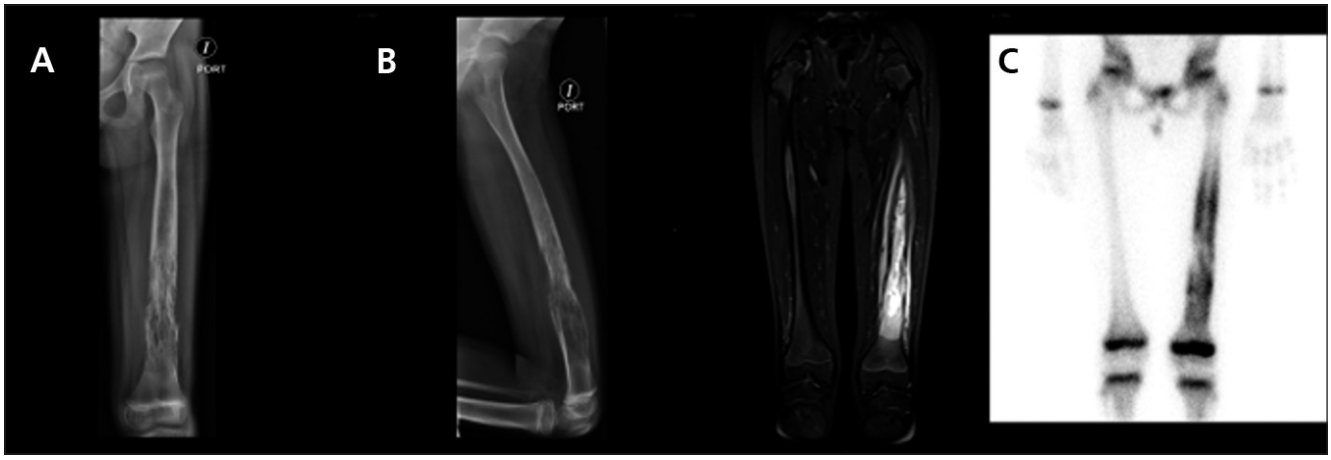

Figure 1. Imaging study of primary lesion **A**) Femur X-ray: infiltrative lytic lesion with poorly defined borders with areas of cortical interruption in the distal diaphysis. Fine periosteal reaction with apparent "onion tissue" morphology. **B**) MRI: extensive bone lesion with disruption of the cortical bone and increased volume of neighboring soft tissues. **C**) Tc-99 bone scan increased irregular uptake in the left femoral shaft, from the infratrocanterean region to the lower metaphysis.

small round blue cell tumors, a group of neoplasms that constitute a diagnostic challenge in the pediatric age since they are tumors with diverse biological nature and different degrees of aggressiveness and determined treatments, so it is very important to have the diagnosis with the greatest possible certainty. This family of tumors is made up of rhabdomyosarcoma, neuroblastoma, Ewing sarcoma/primitive neuroectodermal tumor (ES/PNET), lymphoma, chondrosarcoma, rhabdoid tumor, and osteosarcoma. These tumors present similar histological characteristics and the way to differentiate them is through immunohistochemistry and genetic studies[13,14].

The diagnosis of RMS is based on histologic features showing a small round cell tumor and spindle cells with a high mitotic rate. Immunohistochemistry shows positivity for markers of muscle origin such as vimentin, myogenin, and desmin. Regarding anatomopathological characteristics, RMS is classified into different subtypes with prognostic significance, a subgroup of good prognosis such as botryoid, leiomyosarcomatous, and spindle cell RMS, one of intermediate prognosis as embryonal RMS, and one of poor prognosis as alveolar RMS[15]. Clinically, it manifests as a mass and its symptomatology will depend on the location and the neighboring structures involved.

Genetic alterations also correlate with histologic and prognostic characteristics, thus embryonal RMS present loss of heterozygosity at 11p15.5, while alveolar RMS in 77% of them, present genetic alterations at the level of chromosome 13, with reciprocal translocations t(2;13)q35;q14) or t(1;13)(p36;q14), which compromise the FOXO1 gene generating new fusion proteins that act as transcription factors of greater potency than native proteins, preventing myogenic differentiation and inhibiting apoptosis[16,17].

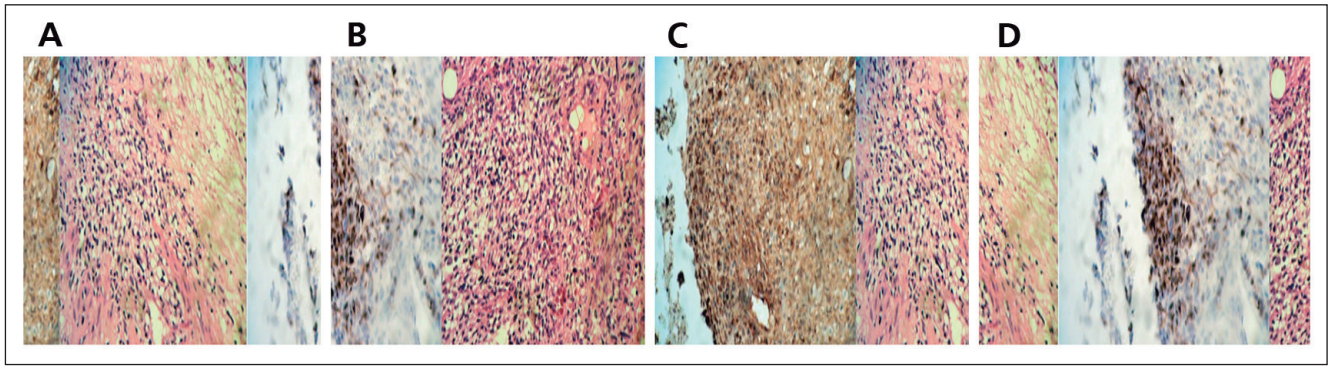

Figure 2. Bone biopsy. **A** and **B**: Hematoxylin-Eosin stain. Small round blue cell tumor; some fused cells. **C**: immunohistochemical staining for desmin. **D**: immunohistochemical (IHC) staining for myogenin. Both IHC stains show intense cytoplasmic staining.

Alveolar RMS represents approximately 15 to 20% of all RMS. It occurs more frequently at school and pubertal age and is more frequently located in the extremities. It is usually a more aggressive tumor, presenting with greater local invasive and metastatic involvement than embryonal RMS[18], and therefore its prognosis is more uncertain, with a higher rate of recurrences and lower survival.

Alveolar RMS associated with positive fusion for FOXO1 gene has a worse prognosis even with aggressive multimodal treatment and the factors that define the outcome are the patient's age, site of origin, tumor size, resectability, presence of metastases in number, sites, and tissues involved as well as regional lymph node involvement. Patients with regional lymph node involvement have a lower survival at five years (43%) than those without involvement (73%[18,19,20]. In this clinical case, the tumor was completely resected, with free margins and there was no regional or distant involvement, which is associated with a better prognosis.

Primary RMS of the bone, either embryonal or alveolar, is very rare. Bone involvement is usually secondary to a soft tissue mass invading neighboring tissues or metastatic involvement in the bone marrow[21]. In the reported case, imaging and biopsy ruled out tumor soft tissue involvement, thus confirming that it was a primary bone tumor.

There are very few cases published in the international literature. The review carried out by the authors only shows 6 patients with primary alveolar RMS of the bone in which there is bone marrow infiltration, without describing a primary tumor that can be located in other areas, however, the presentation as a bone tumor without bone marrow infiltration as in our case is not described[22].

The reported cases of primary alveolar RMS of the bone and positive genetic study of fusion show a better survival compared with those of soft tissue origin, which causes even greater difficulties in the best characterization of this rare type of presentation[22].

Alveolar soft tissue RMS commonly infiltrates the bone marrow, which causes a diagnostic challenge, as it can mimic the symptoms of hematologic malignancy or a primary bone tumor, so a biopsy is mandatory in each case. The differential diagnosis should include Ewing's sarcoma, non-Hodgkin's lymphoma, mesenchymal chondrosarcoma, and osteosarcoma with a small cell variant. While the morphology of the tumor cells is similar, small and round, the osteoid neoplasm is like osteosarcoma and the hyaline cartilage as chondrosarcoma, as well as the intracytoplasmic vacuoles or striation of the tumor cells as RMS.

Besides the careful study of Hematoxylin-Eosin staining, immunohistochemistry including actin, vimentin, desmin, myogenin, CD99, and S100 is of undoubted value in diagnosis, also molecular examination such as flow cytometry (in hematological diseases) or gene fusion analysis (t(11;22) in Ewing or FOXO1 in RMS) are now part of the diagnostic panel[14,16]. Immunohistochemistry in our patient was positive for vimentin, desmin, and myogenin and negative for CD99.

As RMS is a relatively rare entity, national and international cooperative studies have been crucial in the study of this disease. In our country with the support of the National Program of Antineoplastic Drugs (PINDA), and the Latin American regional sphere with the GALOP protocol, multimodal treatment protocols have been developed obtaining an improvement in overall survival, but this has not been reflected in patients with metastatic or recurrent disease, which makes new therapies necessary, such as the approach with immunotherapy, molecular target, or with a different approach in terms of aggressive local therapy if the clinical case allows it[23,24,25].

Conclusion

Primary alveolar RMS of the bone appears to be a distinct clinicopathologic entity, with better apparent biologic behavior, since although it is aggressive in its histology and even with a positive FOXO-1 gene, it has better survival than soft tissue tumors. Our patient, 5 years after her diagnosis and following the treatment according to protocol, has no evidence of disease, which would support this better evolution in this group of patients. It is difficult to predict its evolution due to the low number of cases reported so far. Although infrequent, this tumor should be considered in the differential diagnosis of primary small round blue cell bone tumors.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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References

1. Ognjanovic S, Linaberry A, Charbonneau B, Ross J. Trends in childhood rhabdomyosarcoma Incidence and survival in the United States, 1975-2005. Cancer 2009; 115:4218-26 doi:10.1002/cncr.24465
2. Vallebuona C. Primer informe del Registro Nacional de Cáncer infantil de Chile (menores de 15 años) RENCI. Quinquenio 2007-2011. Minsal 2018 http://www.ipsuss.cl/ipsuss/site/artic/20180117/asocfile/20180117150429/informe_renci_2007_2011registro_nacional_c__ncer_infantildepto_epidemiolog__aminsal2018.pdf última visita 28-04-2020
3. Shern J, Chen L, Chmielecki J, et al. Comprehensive genomic analysis of rhabdomyosarcoma reveals a landscape of alterations affecting a common genetic axis in fusion-positive and fusion-negative tumors. Cancer Discov 2014; 4:2161-31 doi: 10.1158/2159-8290.CD-13-0639.
4. Xia S, Pressey J, Barr F. Molecular pathogenesis of rhabdomyosarcoma. Cancer Biol Therapy 2002;1:97-104. doi.10:4161/cbt.51.
5. Whittle S, Hicks M, Roy A, Vasudevan S, Reddy K, Venkatramani R. Congenital spindle cell rhabdomyosarcoma. Pediatric Blood Cancer 2019; 66: e27935. doi:10.1002/pbc.27935.
6. Meza J, Anderson J, Pappo A, Meyer W. Analysis of prognostic factors in patients with nonmetastatic rhabdomyosarcoma treated on Intergroup Rhabdomyosarcoma Studies III and IV: The Children's Oncology Group, J Clin Oncol 2006; 24(24): 3844-51. doi: 10.1200/JCO.2005.05.3801.
7. Oberlin O, Rey A, Sánchez de Toledo J, et al. Randomized comparison of intensified six-drug versus standard three-drug chemotherapy for high-risk non metastatic rhabdomyosarcoma and other chemotherapy-sensitive childhood soft tissue sarcomas: long term results from the international society of pediatric oncology MMT95 Study. J Clin Oncol 2012; 30: 2457-65. doi: 10.1200/JCO.2011.40.3287.
8. Davis R, Barr F. Fusion genes resulting from alternative chromosomal translocations are overexpressed by gene-specific mechanisms in alveolar rhabdomyosarcoma. Proc Natl Acad Sci USA. 1997; 94 (15): 8047-51. doi: 10.1073/pnas.94.15.8047.
9. Davicioni E, Anderson JR, Buckley JD, Meyer WH, Triche TJ. Gene expression profiling for survival prediction in pediatric rhabdomyosarcomas: a report from the children's oncology group.J Clin Oncol. 2010;28(7):1240-6. doi: 10.1200/JCO.2008.21.1268. Epub 2010 Feb.
10. Dantonello T, Int-Veen C, Schuck A, et al. Survival following disease recurrence of primary localized alveolar rhabdomyosarcoma. Pediatr Blood Cancer 2013; 60: 1267-73. doi: 10.1002/pbc.24488.
11. Malempati S, Hawkins D. Rhabdomyosarcoma: review of the Children's Oncology Group (COG) Soft Tissue Sarcoma Committee experience and rationale for current COG studies. Pediatr Blood Cancer 2012;59:5-10. doi: 10.1002/pbc.24118.
12. Horvai A. Bones, joints and soft tissue tumors. In: Kunmar V, Abbas AK, Aster JC, editors. Robbins & Cotran Pathologic basis of disease. 9th ed. Philadelphia (PA): Elsevier; 2015 . p. 1179-226.
13. Coffin C. The new international rhabdomyosarcoma classification, its progenitoors and considerations beyond morphology. Adv Anat Pathol. 1997;4:1-16
14. Rajwanshi A, Srinivas R, Upasana G. Malignant small round cell tumors. J Cytol 2009;26(1):1-10. doi: 10.4103/0970-9371.54861
15. Walther C, Mayrhofer M, Nilsson J, et al. Genetic heterogeneity in rhabdomyosarcoma revealed by SNP array analysis. Genes Chromosomes Cancer. 2016 Jan;55(1):3-15. doi: 10.1002/gcc.22285. Epub 2015 Oct 20.PMID: 26482321
16. Sorensen PH, Lynch JC, Qualman SJ, et al. PAX3-FKHR and PAX7-FKHR gene fusions are prognostic indicators in alveolar rhabdomyosarcoma: a report from The Children's Oncology Group. J Clin Oncol. 2002;20(11):2672-9.
17. Gallego Melcón S, Sánchez de Toledo Codina J. Rhabdomyosarcoma: present and future perspectives in diagnosis and treatment. Clin Transl Oncol. 2005;7(1):35-41.
18. Weiss AR, Lyden ER, Anderson JR, et al. Histologic and clinical characteristics can guide staging evaluations for children and adolescents with rhabdomyosarcoma: a report from the children's oncology group soft tissue sarcoma committee. J Clin Oncol. 2013;31(26):3226-32.
19. Hibbits E, Chi Y, Hawkins D, et al. Refinement of risk stratification for childhood rhabdomyosarcoma using FOXO1 fusion status in addition to established clinical outcome predictors: a report from the Children´s Oncology Group Cancer Med 2019; 8: 6437-48. doi:10.1002/cam4.2504.
20. Rodeberg D, García-Henriquez N, Lyden E, et al. Prognostic significance and tumor biology of regional lymph node disease in patients with rhabdomyosarcoma: a report from the Children's Oncology Group. J Clin Oncol 2011;29(10):1304-11. doi: 10.1200/JCO.2010.29.4611.
21. Karagiannis P, Guth N, Thoennisen G, et al. Alveolar rhabdomyosarcoma confined to the bone marrow with no identifiable primary tumour using FDG-PET/CT. Clin Sarcoma Res 2015; 5:24. doi:10.1186/s13569-015-0039-6.
22. Balogh P, Bánusz R, Csóka M, Váradi Z, Varga E, Sápi Z. Primary alveolar rhabdomyosarcoma of the bone: two cases and review of the literature. Diag Pathol 2016;11:99. doi:10.1186/s13000-016-0552-9.
23. Hawkins D, Spunt S, Skapek S. COG Soft Tissue Sarcoma Committee. Children´s Oncology Group´s 2013 blueprint for research: soft tissue sarcomas. Pediatr Blood Cancer 2013; 60: 1001-8. doi: 10.1002/pbc.24435.
24. Sepúlveda L, Villarroel M, Reyes M, Tordecilla J, Salgado C, Varas M. Sarcoma de partes blandas. Rabdomiosarcoma. Protocolo Nacional PINDA 2006.
25. Chen C, Dorado Garcia H, Scheer M, Henssen. Current and future treatment strategies for rhabdomyosarcoma. Front Oncol 2019;9: 1458. doi: 10.3389/fonc.2019.01458.