Pseudomyogenic hemangioendothelioma of bone with rare WWTR1-FOSB fusion gene: Case report and literature review

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INTRODUCTION

Pseudomyogenic hemangioendothelioma (PMHE) is an uncommon vascular neoplasm of intermediate malignant potential that rarely arises in bone. SERPINE1-FOSB fusion gene occurs frequently in PMHE of bone; however, WWTR1-FOSB fusion gene is rarely reported. The prognostic and therapeutic significance of these gene rearrangements is unclear and needs to be investigated further.

Pseudomyogenic hemangioendothelioma (PMHE) is a rare endothelial neoplasm of intermediate malignant potential that usually arises in the soft tissues of the lower and upper extremities.1-4 Its occurrence in bone is a rare event. To the best of our knowledge, only 27 cases of primary PMHE of bone have been reported so far.1-17 (Table 1). Few of those reported cases were found to harbor the balanced translocation t(7;19)(q22;q13) producing fusion between SERPINE1 and FOSB genes,10,12 and only one case was found to carry WWTR1-FOSB fusion gene.17 Herein, we present the second case of primary PMHE of bone with WWTR1-FOSB fusion gene.

CASE PRESENTATION

A previously healthy 7-year-old girl presented to the clinic with intermittent pain of the right thigh for two-year duration. The pain was more severe at night. It was not associated with fever, weight loss, or other constitutional symptoms. Analgesics were given initially which relieved her symptoms temporarily; however, she started to feel pain at her right knee after an accident of falling. X-ray was performed, which revealed a well-demarcated radiolucent lytic lesion arising from the metaphysis of the right distal femur with cortical thinning. However, no periosteal reaction or soft tissue involvement was identified (Figure 1). A needle core
biopsy was taken from the lesion. Histopathology shows a tumor composed of infiltrative sheets and fascicles of plump spindle and epithelioid cells (Figure 2A and 2B). In some areas, the tumor is admixed with reactive woven bone and osteoclast-type multinucleated giant cells (Figure 2C and 2D). Some of the tumor cells are elongated and have dense eosinophilic cytoplasm with strap cell–like appearance (Figure 2E). Abundant numbers of neutrophils in the stroma are present. No stromal hyalinization or myxohyaline changes are identified. No vasoformative areas are seen. The tumor cells show mild nuclear atypia with few mitotic figures. However, there are no atypical mitoses or tumor cell

**TABLE 1** Cases of Primary Pseudomyogenic Hemangioendothelioma of Bone

| Case | Author (ref) | Year | Age | Sex | Site                          | Multifocal | Gene rearrangement                  |
|------|--------------|------|-----|-----|-------------------------------|------------|-------------------------------------|
| 1    | Hornick et al⁴  | 2011 | 35  | Male | Upper extremity (finger)      | No         | Not performed                       |
| 2    | Sheng et al⁵ | 2012 | 10  | Female | Left lower extremity            | Yes        | Not performed                       |
| 3    | McGinity et al⁶ | 2013 | 25  | Male | Thoracic spine                 | No         | Not performed                       |
| 4    | Righi et al⁷  | 2014 | 25  | Male | Left upper extremity (distal radius) | No         | Not performed                       |
| 5    | Righi et al⁷  | 2014 | 66  | Female | Left lower extremity            | Yes        | Not performed                       |
| 6    | Shah et al⁸   | 2015 | 86  | Male | Lower extremity                | Yes        | Not performed                       |
| 7    | Joseph et al⁹ | 2015 | 45  | Male | Right pelvis (Ileum)          | No         | Not performed                       |
| 8    | Inyang et al¹⁰ | 2016 | 59  | Male | Thoracic spine                 | Yes        | Not performed/failed                |
| 9    | Inyang et al¹⁰ | 2016 | 19  | Male | Right lower extremity          | Yes        | Not performed/failed                |
| 10   | Inyang et al¹⁰ | 2016 | 47  | Male | Left lower extremity           | Yes        | Not performed/failed                |
| 11   | Inyang et al¹⁰ | 2016 | 14  | Male | Left upper extremity           | Yes        | t(7;19)(q22;q13) with SERPINE1-FOSB fusion |
| 12   | Inyang et al¹⁰ | 2016 | 74  | Male | Spine and pelvis               | Yes        | Not performed/failed                |
| 13   | Inyang et al¹⁰ | 2016 | 20  | Male | Left lower extremity           | Yes        | Not performed/failed                |
| 14   | Inyang et al¹⁰ | 2016 | 66  | Male | Spine and pelvis               | Yes        | Not performed/failed                |
| 15   | Inyang et al¹⁰ | 2016 | 12  | Male | Left lower extremity           | Yes        | t(7;19)(q22;q13) with the SERPINE1-FOSB fusion |
| 16   | Inyang et al¹⁰ | 2016 | 26  | Male | Multiple                      | Yes        | t(7;19)(q22;q13) with the SERPINE1-FOSB fusion |
| 17   | Inyang et al¹⁰ | 2016 | 5   | Female | Right lower extremity and pelvis | Yes        | Not performed/failed                |
| 18   | Ye et al¹¹    | 2016 | 14  | Female | Left lower extremity          | Yes        | Not performed                       |
| 19   | Ozeki et al¹² | 2017 | 15  | Male | Left lower extremity and spine | Yes        | t(7;19)                            |
| 21   | Pradhan et al¹³ | 2018 | 9   | Female | Lower extremity (proximal femur) | No         | Failed                             |
| 22   | Pradhan et al¹³ | 2018 | 53  | Male | Upper extremity (ulna)        | Yes        | Negative for t(7;19)               |
| 23   | Pradhan et al¹³ | 2018 | 16  | Male | Lower extremity (tibia)       | No         | Failed                             |
| 24   | Squillaci et al¹⁴ | 2018 | 46  | Female | Right lower extremity (patella) | No         | Not performed                      |
| 25   | Otani et al¹⁵ | 2019 | 20  | Female | Left lower extremity          | Yes        | Not performed                      |
| 26   | Dianat et al¹⁶ | 2019 | 63  | Male | Sacrum                        | No         | Not performed                      |
| 27   | Panagopoulos et al¹⁷ | 2019 | 33  | Female | Sacrum and spine             | Yes        | WWTR1-FOSB fusion                  |
| 28   | Current case  | 2020 | 7   | Female | Right lower extremity (distal femur) | No         | WWTR1-FOSB fusion                  |
necrosis. By immunoperoxidase stains, the tumor cells demonstrate reactivity for the vascular markers CD31 and ERG, and the epithelial marker cytokeratin AE1/AE3 (Figure 3A-3C). They also show diffuse and strong nuclear reactivity for FOSB antibody (Figure 3D), but are negative for CAMTA1 and TFE3. A final diagnosis of pseudomyogenic hemangiendothelioma was rendered.

Next-generation sequencing (NGS) was performed to identify possible targeted therapies for the patient’s tumor. Genomic DNA was extracted from formalin-fixed paraffin-embedded (FFPE) tissue by macrodissection technique. A sarcoma-targeted gene fusion panel was used to test for the presence of rearrangements in 138 targeted genes. The tumor was found to carry WWTR1-FOSB fusion gene. Fusion/transcript variant junction locations and mutation nomenclature are based on RefSeq accession numbers: NM_015472 and NM_006732. The fusion/transcript variant junction location and the corresponding genomic coordinates within the WWTR1 gene occur in exon 4 at genomic position Chr3:g.149260122 and within the FOSB gene occur in exon 2 at genomic position Chr19:g.45973887.

Whole-body magnetic resonance imaging (MRI) and positron emission tomography (PET) scan were performed and revealed no evidence of distant metastasis. The patient underwent partial excision of the affected bone cortex with overlying muscle (vastus intermedius), along with extended curettage of the lesion. This was followed by filling of the defect using cancellous bone graft with internal fixation by plates and screws that do not cross the epiphysial plate to avoid leg length discrepancy and growth retardation. Postoperative X-ray showed satisfactory impaction of the bone graft and plate fixation (Figure 4). The patient was followed up for 6 months after operation, and there was no evidence of local recurrence during that period. She is still now on regular follow-up.

3 | DISCUSSION

PMHE is a rare vascular tumor with distinct clinical, pathologic, and molecular features. In 2003, the tumor was recognized as a distinctive entity under the name of “epithelioid sarcoma–like hemangiendothelioma” by Billing et al, due to combined features of morphological similarity with epithelioid sarcoma and immunoreactivity for vascular immunohistochemical markers.1 The term “pseudomyogenic hemangiendothelioma” was first proposed by Hornick and Fletcher in 2011, when they published a study of 50 cases of this tumor with extensive analysis of the clinicopathological and immunophenotypic features.4 The term was then adopted by the current World Health Organization (WHO) classification of tumors of soft tissue and bone in 2013.2

PMHE usually affects young adult males with a predilection for the lower limb. Multifocal presentation is not uncommon. However, in our case the tumor was unifocal. Morphologically, PMHE is an infiltrative neoplasm formed by sheets and loose fascicles of plump spindle and epithelioid cells having abundant bright eosinophilic cytoplasm. The tumor cells usually exhibit mild nuclear pleomorphism with vesicular nuclei and prominent nucleoli. Some cells have rhabdomyoblast-like appearance with dense eosinophilic cytoplasm and peripherally located nuclei. Occasionally, prominent stromal neutrophils are present in the stroma.

PMHE is a locally aggressive tumor with high risk for local recurrence following surgical excision; however, it is a rarely metastasizing neoplasm.14 It is essential to differentiate this tumor from other epithelioid soft tissue neoplasms including epithelioid hemangioma (EH), epithelioid hemangiendothelioma (EHE), epithelioid sarcoma (ES), and epithelioid angiosarcoma (EAS). Unlike PMHE, EH is characterized by well-defined proliferation of vascular spaces lined by bland epithelioid endothelial cells with hobnailing into the lumen. The stroma usually contains varying numbers of eosinophils. Although the tumor cells in EH can show nuclear reactivity for FOSB antibody, cytokeratin AE1/AE3 is usually negative or shows patchy weak positivity. There is a considerable overlap between PMHE

FIGURE 1 Plain X-ray shows a well-demarcated radiolucent lytic lesion in the metaphysis of the distal femur (blue arrow). There is no soft tissue involvement.

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and the spindle cell variant of EH of bone. Both tumors share similar clinical presentation, morphology, and immunophenotype, which make the distinction between them difficult and challenging. Both tumors commonly present as multifocal lesions, have prominent spindle cell component, and demonstrate immunoreactivity for cytokeratin and FOSB. Currently, the main distinguishing feature is the ability to demonstrate vasoformative areas lined by “tombstone”-like cuboidal endothelial cells, a finding that is compatible with spindle cell EH. We were not able to demonstrate vasoformative areas in our case.

The distinction between PMHE and EHE can be very challenging. EHE is composed of tumor cells that have characteristic intracytoplasmic lumina containing red blood cells, embedded in myxohyaline stroma. EHE is characterized by recurrent t(1;3)(p36.3;q25) translocation, resulting in WWTR1-CAMTA1 fusion gene, and another subset of cases harbor YAP1-TFE3 fusion gene. Therefore, the tumor cells in EHE demonstrate diffuse nuclear expression for CAMTA1 and less commonly TFE3 by immunohistochemistry. Unlike PMHE, FOSB is negative in EHE. ES lacks the fascicular growth pattern. The tumor cells in ES are immunoreactive for CD34 and epithelial membrane antigen (EMA), but negative for FOSB. The most essential feature is loss of INI-1 nuclear expression in ES, which is intact in PMHE. The tumor cells in EAS are arranged in freely anastomosing vascular channels lined by markedly atypical tumor cells with frequent mitotic figures including atypical forms. FOSB is negative in EAS.

PMHE has distinct molecular profile. The balanced translocation t(7;19)(q22;q13) producing fusion of SERPINE1 and FOSB genes is well documented. This translocation, which has not been detected in any other bone or soft tissue tumor, results in fusion of SERPINE1 and FOSB genes, which leads to strong expression of FOSB. This gene product can be detected by immunohistochemistry. In 2018, Agaram et al and Zhu et al reported some cases of PMHE with recurrent ACTB-FOSB gene fusions. Recently, Panagopoulos et al reported a case of a 33-year-old woman with multifocal PMHE involving the sacrum and spine with novel WWTR1-FOSB fusion gene, which was the first case of primary PMHE of bone carrying this fusion gene. In our case, the tumor was unifocal and harbors similar fusion gene detected by NGS, which revealed a fusion between WWTR1.
gene located on exon 4 of chromosome 3 with \textit{FOSB} gene on exon 2 of chromosome 19.

It is essential to mention that \textit{WWTR1-FOSB} fusion is not specific for PMHE. In a study performed by Huang et al, \textit{FOS} gene rearrangement was found to be present in a third of epithelioid hemangioma (EH) cases across different locations and histologic variants with more prevalence in cellular EH and intraosseous lesions.\textsuperscript{20,26} The fusion genes detected in EH in that study include \textit{ZFP36-FOSB} and \textit{WWTR1-FOSB}.

In summary, we are presenting the second case of primary PMHE of bone with \textit{WWTR1-FOSB} fusion gene. Several fusion genes have been detected in PMHE. All these fusion genes lead eventually to upregulation of \textit{FOSB} transcription factor, which makes it a useful immunohistochemical diagnostic marker for PMHE. The relationship between the various gene rearrangements occurring in PMHE and the clinicopathological features as well as the biological behavior of the tumor is still unclear, and further research should be pursued.

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\textbf{CONFLICT OF INTEREST}

The authors declare that they have no competing interests.

\textbf{AUTHOR CONTRIBUTIONS}

KAM: conceived and designed the idea, performed literature review, wrote the manuscript, and overall organized the case report. JTM: performed further immunohistochemical stains and molecular studies on the case. AME: provided clinical information. AA: reviewed the case and the manuscript. IAB: reviewed the manuscript and supervised the project.
ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Institutional Review Board of the Medical Research Council, Hamad Medical Corporation, Qatar, reviewed the protocol and approved it under the number (MRC-04-20-250). Informed consent has been waived by the Institutional Review Board (IRB).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Billings SD, Folpe AL, Weiss SW. Epithelioid sarcoma-like hemangioendothelioma. Am J Surg Pathol. 2003;27(1):48-57.
2. Fletcher CDM, Bridge JA, Hogendoorn PCW, et al. WHO Classification of Tumors of Soft Tissue and Bone. In: Merteras F, ed. Pathology and Genetics of Tumors of Soft Tissue and Bone, 4th edn. Lyon: IARC Press; 2013:153–154.
3. Al-Qaderi A, Mansour AT. Pseudomyogenic Hemangioendothelioma. Arch Pathol Lab Med. 2019;143(6):763-767.
4. Hornick JL, Fletcher CDM. Pseudomyogenic hemangioendothelioma: a distinctive, often multicentric tumor with indolent behavior. Am J Surg Pathol. 2011;35:190-201.
5. Sheng WQ, Wang J. Primary pseudomyogenic hemangioendothelioma of bone. Histopathology. 2012;61:1219-1224.
6. McGinity M, Bartanusz V, Dengler B, et al. Pseudomyogenic hemangioendothelioma (epithelioid sarcoma-like hemangioendothelioma, fibroma-like variant of epithelioid sarcoma) of the thoracic spine. Eur Spine J. 2013;22:s506-s511.
7. Righi A, Gambarotti M, Picci P, et al. Primary pseudomyogenic hemangioendothelioma of bone: report of two cases. Skeletal Radiol. 2015;44:727-731.
8. Shah AR, Fernando M, Musson R, Kotnis N. An aggressive case of pseudomyogenic haemangioendothelioma of bone with pathological fracture and rapidly progressive pulmonary metastatic disease: case report and review of the literature. Skelet Radiol. 2015;44:1381-1386.
9. Joseph J, Wang WL, Patmana M, et al. Cytotoxic and targeted therapy for treatment of pseudomyogenic hemangioendothelioma. Clin Sarcoma Res. 2015;5:22.
10. Inyang A, Mertens F, Puls F, et al. Primary pseudomyogenic hemangioendothelioma of bone. Am J Surg Pathol. 2016;40:587-598.
11. Ye C, Yu X, Zeng J, et al. Pseudomyogenic hemangioendothelioma secondary to fibrous dysplasia of the left lower extremity in a 14-year-old female: a case report. World J Surg Oncol. 2016;14:198-202.
12. Ozeki M, Nozawa A, Kanda K, et al. Everolimus for treatment of pseudomyogenic hemangioendothelioma. J Pediatr Hematol Oncol. 2017;39:e328-331.
13. Pradhan D, Schoedel K, McGough RL, et al. Pseudomyogenic hemangioendothelioma of skin, bone and soft tissue - a clinicopathological, immunohistochemical, and fluorescence in situ hybridization study. Hum Pathol. 2018;71:126-134.
14. Squillaci S, Pitino A, Spairani C, Rassu PC, Chiapuzzo E, Kutzner H. Primary pseudomyogenic hemangioendothelioma of bone: case report and review of the literature. Pathologica. 2018;110:96-101.
15. Otani S, Nakayama R, Sekita T, et al. Pseudomyogenic hemangioendothelioma of bone treated with denosumab: a case report. BMC Cancer. 2019;19:872.
16. Dianat S, Yousaf H, Murugan P, et al. Pseudomyogenic hemangioendothelioma—a case report and review of the literature. Radiol Case Rep. 2019;14:1228-1232.
17. Panagopoulos I, Lobmaier I, Gorunova L, Heim S. Fusion of the genes WWTR1 and FOSB in pseudomyogenic hemangioendothelioma. Cancer Genom Proteom. 2019;16:293-298.
18. Keel SB, Rosenberg AE. Hemorrhagic epithelioid and spindle cell hemangioma: a newly recognized, unique vascular tumor of bone. Cancer. 1999;85(9):1966-1972.
19. Keil F, Dietmaier W, Hofstetter P, Hillmann A, Evert M. ZFP36-FOSB fusion in a haemorrhagic epithelioid and spindle cell haemangioma of bone: is there a family of FOSB-rearranged vascular neoplasms of the bone? Histopathology. 2020;76(3):490-493.
20. Huang S-C, Zhang L, Sung Y-S, et al. Frequent FOS gene rearrangements in epithelioid hemangioma: a molecular study of 58 cases with morphologic reappraisal. Am J Surg Pathol. 2015;39:1313-1321.
21. Lee SJ, Yang WI, Chung WS, Kim SK. Epithelioid hemangioendotheliomas with TFE3 gene translocations are compositive with CAMTA1 gene rearrangements. Oncotarget. 2016;7(7):7480-7488.
22. Hung YP, Fletcher CD, Hornick JL. FOSB is a Useful Diagnostic Marker for Pseudomyogenic Hemangioendothelioma. Am J Surg Pathol. 2017;41(5):596-606.
23. Walther C, Tayebwa J, Lilijebjörn H, et al. A novel SERPINE1-FOSB fusion gene results in transcriptional up-regulation of FOSB in pseudomyogenic haemangioendothelioma. J Pathol. 2014;232:534-540.
24. Agaram NP, Zhang L, Cotzia P, Antonescu CR. Expanding the spectrum of genetic alterations in pseudomyogenic haemangioendothelioma with recurrent Novel ACTB-FOSB gene fusions. Am J Surg Pathol. 2018;42:1653-1661.
25. Zhu G, Benayed R, Ho C, et al. Diagnosis of known sarcoma fusions and novel fusion partners by targeted RNA sequencing with identification of a recurrent ACTB-FOSB fusion in pseudomyogenic haemangioendothelioma. Mod Pathol. 2018;32:609-620.
26. Murshed K, Faraghy Al. Multifocal Epithelioid Hemangioma of the Penis in a 4-Year-Old Child: A Case Report. Am J Dermatopathol. 2020;42:372-374.