



Malignant Angiomatoid Fibrous Histiocytoma: a separate entity or just the visible part of an iceberg? Case Report of Uncommon Tumor and Brief Review of Literature

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Abstract

Introduction: Angiomatoid fibrous histiocytoma (AFH) is a rare soft-tissue neoplasm often arising in children and young adults. They commonly occur in somatic soft tissue, mainly the upper and lower extremities. AFH is a translocation associated neoplasm, with the majority of cases positive for *EWSR1-CREB1* translocation. The tumor was initially described as “malignant” AFH. However, it has a relatively rare chance of metastasis. AFH shows a broad spectrum of morphological patterns, and metastatic lesions may or may not show malignant features.

Report: We report a case of a 12-year-old female who presented with a left supraclavicular mass that was initially diagnosed as a benign fibrous histiocytoma. The mass was excised with clear surgical margins. Six years later, the patient presented with multiple retroperitoneal masses and later succumbed to metastatic disease. Molecular studies confirmed an *EWSR1-CREB1* fusion gene in the primary and metastatic lesions. The culmination of these features led to the diagnosis of a metastatic angiomatoid fibrous histiocytoma.

Conclusion: AFH is a rare neoplasm with a spectrum of morphological characteristics and a vast array of immunophenotypical profiles. This can make the diagnosis of AFH challenging. Few cases of metastatic AFH have been reported in literature. However, when these lesions do metastasize, they are often fatal. It is our hope that this report raises awareness of what remains an unmet need in the diagnosis and management of “angiomatoid fibrous histiocytoma with malignant features.”

Keywords: Angiomatoid fibrous histiocytoma, metastasis, morphology, translocation, lung, retroperitoneal, treatment

Abbreviations

AFH: Angiomatoid fibrous histiocytoma, ASMA: α -Smooth Muscle Actin, EMA: Epithelial Membrane Antigen, CT: Computed Tomography, MRI: Magnetic Resonance Imaging, PPMS: Primary Pulmonary Myxoid Sarcoma, IL-6: Interleukin-6

Introduction

Angiomatoid fibrous histiocytoma (AFH) is a soft tissue neoplasm that most often occurs in the deep dermis and subcutis of extremities. It affects a wide age range, but 88% of cases occur in patients 30 years or younger [1]. The histogenesis of

this tumor remains unclear. Microscopically, the tumors are characterized by spindle/histiocytoid cells, pseudoangiomatous spaces, peritumoral lymphoplasmacytic cuffing, and a fibrous pseudocapsule. However, there are many morphological variants, including clear cells, small cells, and rhabdomyoblast like cells [2]. This can lead to multiple challenging differential diagnoses. Immunohistochemically, AFH is frequently positive for vimentin, desmin, α -smooth muscle actin (ASMA), epithelial membrane antigen (EMA), CD68, and CD99 [2,3]. More recently, molecular studies have proven crucial to the diagnosis of AFH. Three characteristic translocations have been associated with this neoplasm, including *EWSR1-CREB1*, *EWSR1-ATF1*, and *FUS-ATF1* [4]. *EWSR1-CREB1* has been demonstrated to be the predominant translocation in the majority of these tumors [5].

AFH was initially described as “malignant,” but has since been described as a relatively benign condition. Few cases of metastasis have been reported. However, AFH can metastasize to the lung and is often fatal. There have been 4 cases (including this one) that have a confirmed *EWSR1-CREB1* translocation in the primary and metastatic lesion. Tumors that metastasize show a variety of atypical features (pleomorphism, high mitotic figures, and necrosis); however, others do not. Therefore, pathologists and clinicians need to be aware of this tumor’s spectrum of features and risk of metastasis. Because this tumor has a chance of local recurrence and metastasis, wide local excision has been the mainstay of treatment.

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Case Presentation

A 12-year-old female with no past medical history presented with a slowly growing mass in the left supraclavicular area measuring 2.5 cm. The mass was present for at least two years but only recently began enlarging. At the time of presentation, she had associated pyrexia, anemia, and malaise. She had no significant family history. Computed tomography (CT) scan revealed a heterogeneous mass with possible cystic and enhancing components. Magnetic resonance imaging (MRI) showed non-specific findings including multiple internal cystic areas, enhancing fibrous pseudocapsule markedly hypointense on T1 and T2, foci of susceptibility artifacts representing hemosiderin, and some areas of suggested fluid levels. The mass was excised. The gross specimen measured 1.8 cm and was well-circumscribed. It involved the deep dermis but did not extend to the skin.

Microscopically, the tumor mass showed a false appearance of a lymph node with metastatic tumor, and a fibrous pseudocapsule was also noted (Figure 1A). The tumor mass was composed of ovoid and spindle cells with bland, vesicular nuclei. In addition, lymphoplasmacytic infiltrate with intervening blood-filled cystic spaces were also noted (Figure 1B). There were scattered highly atypical cells with marked pleomorphism (Figure 1C). Mitotic activity was difficult to find, and 2 mitosis/10 HPF were identified as well as rare foci of necrosis. Immunohistochemistry was not specific and was positive only for vimentin, bcl-2, and focal scattered cells positive for CD99 and ASMA. Although rare foci of pleomorphism, necrosis, and few mitoses were noted, it was reported as not significant enough for the diagnosis of malignancy. The diagnosis of benign fibrous histiocytoma was concluded. All surgical margins were free of tumor, and the patient received no adjuvant treatment after surgical excision but only post-excisional monitoring.

Six years later, the patient reported severe abdominal pain. CT and MRI studies reported multiple retroperitoneal masses. Biopsy from one of the masses showed similar histomorphology to the initial supraclavicular tumor, but with significant nuclear malignant features. In addition, moderate foci of necrosis and increased mitotic activity up to 6 mitosis/10 HPF were also noted. The histomorphology was consistent with a malignant

neoplasm, however, possible carcinoma, neuroendocrine, lymphoma, or melanoma were less likely based on negative pancytokeratin, synaptophysin, CD45, S-100, and Melan-A. Studies were performed on the metastatic tumor as well as on sections from a paraffin block from the original tumor. Although a diagnosis of “unclassified undifferentiated sarcoma” may sound appropriate here, the histomorphology and minimum support of immunohistochemistry were more consistent with an aggressive malignant form of AFH. Molecular testing was suggested on the current and prior tumor. The *EWSR1-CREB1* fusion gene was identified in both tumors. This finding supported the diagnosis of AFH with malignant features. Due to advanced metastasis, the patient was not a candidate for surgical intervention and was administered chemotherapy in the form of gemcitabine and docetaxel. Unfortunately, the patient expired six months later due to extensive metastatic disease, predominantly to the lung, and multiple organ failure despite the induction of systemic chemotherapy.

Discussion

Angiomatoid fibrous histiocytoma (AFH) is a rare soft tissue neoplasm. It was first described by Enzinger [6] in 1945 as angiomatoid “malignant” fibrous histiocytoma. Since then, the word “malignant” has been removed from the name because the neoplasm does not classically behave in this manner. AFH is sometimes challenging to diagnose because it has few unifying components, relatively non-specific morphology, and diverse immunohistochemical markers. It can frequently be misdiagnosed as a hemangioma, synovial sarcoma, dermatofibroma, or metastatic tumor to a lymph node. More recently, molecular techniques have been used to aid in the diagnosis of this tumor as demonstrated in our case.

AFH is found primarily in the deep dermis and subcutis in the upper and lower extremities. However, there have been cases with primary AFH in extrasomatic tissues such as the lungs, mediastinum, retroperitoneum, vulva, and ovary [2]. The classic somatic AFH has a median age range from 12 to 18 years, with 80% under the age of 20 vs. extrasomatic, which has a median age of 35 years. Local recurrence for classic soft tissue AFH is 10-15%, whereas extrasomatic AFH is around 28%. However, this may be due to the difficulty in resecting these tumors when

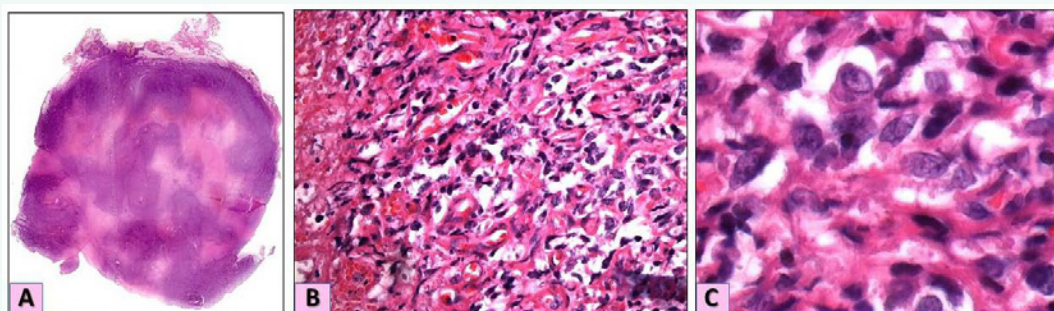


Figure 1 A) The tumor mass has the false appearance of a lymph node with metastatic tumor. A fibrous pseudocapsule is also noted (H&E Scanning magnification). B) The tumor is composed of ovoid and spindle cells with bland, vesicular nuclei. In addition, lymphoplasmacytic infiltrate with intervening blood-filled cystic spaces are noted (H&E X40). C) Scattered highly atypical cells with marked pleomorphism (H&E X40).



they are in challenging locations. Classic AFH typically has a median size of 2-2.8 cm [2]. Patients are often symptomatic at presentation, with common symptoms including pyrexia, weight loss, chills, malaise, and anemia. These masses are typically not painful. They have a gender ratio of 1.3 females to males [3]. The histogenesis of this tumor remains unclear with multiple proposed theories. Various translocations have been discovered in many of these tumors. These likely contribute to the initial steps of tumor formation [7].

Grossly, most tumors are characterized by circumscribed, multinodular or multicystic, hemorrhagic, grayish-yellow to white lesions [4,6]. Microscopically, classic features of AFH have been previously well described. These include: 1) multinodular growth of spindle or histiocytoid cells with distinctive syncytial appearance, 2) pseudoangiomatous spaces filled with blood, 3) a fibrous pseudocapsule with or without hemosiderin deposition, 4) peritumoral lymphoplasmacytic cuffing with occasional germinal center formation [4,8]. AFH is known to exhibit a spectrum of morphological findings. Chen et al. [2] described AFH with diverse morphological patterns, including clear cells, small cells, and rhabdomyoblast like cells, pulmonary edema-like pattern, and tumor cells forming cords in a myxoid stroma. According to Thway [4], the only unifying feature of AFH is "sheets and short fascicles of ovoid, epithelioid, or spindle cells with bland, vesicular nuclei."

Immunohistochemically, AFH is frequently positive for vimentin, desmin, ASMA, EMA, CD68, and CD99 [2]. AFH are frequently negative for cytokeratin, CD21, CD34, CD35, CD56, S100, GFAP, and lysozyme. Desmin is the most relevant immunohistochemical finding occurring in ~50% of cases, but not in all cases [3,9]. These positive immunohistochemical markers are not specific to AFH. Malignant fibrous histiocytoma is often positive for vimentin and occasionally positive for desmin, CD68, CD34, ASMA, muscle-specific actin, and EMA [10]. Our case was positive for vimentin, bcl-2, and one retroperitoneal biopsy sample was positive for CD99. The staining was equivocal for OCT2, BOB.1, bcl-6. Rehki et al. [11] also report a case with positive bcl-2, which is a regulator protein of cell death that inhibits the actions of pro-apoptotic proteins promoting cell survival. Our case was negative for the following: CK, CK19, CK7, EMA, S-100, actin, myogenin, CD31, CD34, HHV8, MNF116, CD45, CD1a, CD138, MUM18, desmin, CD21, lysozyme, CD68, CD30, CK-MNF, ER, PGR, CD35, AML, HECA, CD123, CD117, perforin, and synaptophysin. This immunohistochemical profile essentially rules out possible carcinoma, neuroendocrine, lymphoma, or melanoma, and is supportive of the diagnosis of sarcoma.

Over the past decade, AFH has been increasingly described as a translocation associated neoplasm. There are three characteristic translocation created fusion genes associated with AFH: *EWSR1-CREB1* t(2;22), *EWSR1-ATF1* t(12;22), and *FUS-ATF1* t(12;16) [4]. *EWSR1-CREB1* has been demonstrated to be the predominant translocation in AFH [5]. However, *EWS-ATF1* seems to be more predominant in extrasomatic AFH [2]. *EWSR1* and *FUS* are RNA binding proteins, and *CREB1* and *ATF1* are cAMP response binding proteins. Fusions among these genes are seen in a variety of tumors, including gastrointestinal clear

cell sarcoma and primary pulmonary myxoid sarcoma [4]. While these fusion proteins are identical, they are found in separate tumors, suggesting unknown downstream genetic events that explain these two phenotypes [12]. Rossi et al. [12] suggest that in vitro studies with transfection of *EWSR1-ATF1/CREB1* fusion gene into different cell lineages could help clarify the pathological mechanism. Among cases of AFH that were positive for the *EWSR1-CREB1* translocation, one case had significant pleomorphism. However, this patient is recurrence-free after seven years [12]. Yet, the *EWSR1-CREB1* translocation has been seen in three cases where metastasis and death have occurred [13], including this case. Therefore, while *EWSR1-CREB1* has shown to be a reliable diagnostic tool for AFH, its utility in prognosis is unclear.

AFH has a diverse spectrum of immunophenotypic and morphological characteristics that lead to a broad differential diagnosis. This neoplasm can mimic benign diseases such as dermatofibroma due to the abundance of fibrohistiocytic cells. Many tumors are positive for desmin, leading to a diagnosis of rhabdomyosarcoma or leiomyosarcoma. However, strap cells and rhabdoid cytoplasm, which are usually seen in rhabdomyosarcoma, are not present in AFH. AFH has characteristic cavernous spaces filled with blood. This has led to incorrect diagnoses of vascular tumors such as hemangiomas, Kaposi sarcoma, or angiosarcoma. Aneurysmal benign dermal fibrous histiocytoma has a similar fibrous histiocytoma appearance with pooling of blood and also lacks endothelium. However, it usually lacks the lymphoplasmacytic infiltrate and fibrous capsule characteristic of AFH. One of the defining features of AFH is peritumoral lymphoplasmacytic cuffing with occasional germinal center formation. This can be mistaken for metastatic mesenchymal tumor to a lymph node. However, true lymph node architectural features including capsule are not present in AFH. AFH may also show pleomorphism, so undifferentiated pleomorphic sarcoma should also be on the list of differentials. There are also small round cell tumor variants of AFH that could be mistaken for Ewing's sarcoma [2,9]. Primary pulmonary myxoid sarcoma (PPMS) is a rare tumor with a reticular pattern and myxoid component that can harbor *EWSR1-CREB1* fusion protein [14]. Cases of primary pulmonary AFH with reticular patterns and *EWSR1-CREB1* fusion proteins have been reported as well [15]. This can further confuse diagnoses; however, PPMS has a more abundant myxoid stroma and does not express desmin [14]. EMA positivity can lead to the inaccurate diagnosis of synovial sarcomas or PPMS [4].

Angiomatoid fibrous histiocytoma is known as a low-grade malignancy with rare metastatic potential. Due to the rarity of this tumor, there is little data on metastasis rates. Examination of the two largest case studies suggests the rate of metastasis is less than 2% [3,16]. Enzinger [6] initially described metastatic lesions as having increased pleomorphism compared to the primary tumor. A review of literature suggests few cases of metastatic AFH. The timing of metastasis has been reported to vary between 5 months and 16 years after initial resection [17]. Common sites of metastasis include regional lymph nodes, lung, and occasionally the brain [6,16]. Nine cases of metastatic AFH to the lung have been reported, seven proving fatal [6,13,16,18,19],



one unknown follow-up [20], and one newly diagnosed [21]. This does not include the current case, with the patient succumbing to metastatic disease involving the lung.

Thway [22] originally described the first case of metastatic AFH genetically proven by RT-PCR, by showing *EWSR1-CREB1* in the primary and metastatic lesion. Since then, there have been three additional cases of molecular proven metastatic AFH with *EWSR1-CREB1* reported in literature, including our current case [13]. There is not enough data to support a specific translocation associated with metastasis. Previous cases of metastatic disease were limited by the technology of that time; however, they may have had the *EWSR1-CREB1* fusion gene. Saito et al. [13] describe a fatal case of metastatic AFH to the lung that harbored the *EWSR1-CREB1* translocation. The metastatic lesion displayed pleomorphic tumor cells that contained increased copies of rearranged *EWSR1* genes vs. non-pleomorphic areas [13]. They suggest this may be helpful in future AFH to predict local recurrence and metastasis [13].

Metastatic lesions frequently show atypical morphological features; however, sometimes, they do not. Matsumura et al. [19] describe a case of two distant AFH metastases that showed large pleomorphic cells with hyperchromatic nuclei and high proliferative activity (>10/10 HPF, Ki-67 >10%). Each of these tumors showed translocations involving the *EWSR1* gene. In contrast to these findings, Thway [22] described the first metastatic lesion with confirmed *EWSR1-CREB1*. This did not show any atypical features. Atypical morphological features are not necessarily indicative of metastasis. Shi et al. [23] describe cases of AFH that showed giant hyperchromatic nuclei, increased mitotic figures, focal necrosis, and multinucleated giant cells. All of these patients were metastasis-free after a median duration of 48 months.

Due to the chance of local recurrence or metastasis, primary management of AFH is wide local resection. Chemotherapy and radiation can be added for unresectable or metastatic disease. However, chemotherapy has not been successful in the few cases of distant metastasis including current case [13,19]. Systemic symptoms have been reported to resolve after removal of the mass [2]. The *EWSR1-CREB1* fusion gene in AFH has been shown to enable increased production of Interleukin-6 (IL-6) [24]. Tocilizumab (IL-6 receptor antibody), primarily used for rheumatoid arthritis, has recently been implemented into a treatment plan for *EWSR1-CREB1* positive AFH tumors [25]. All patients with AFH, especially ones with malignant features, require close follow-up.

There are no distinguishing clinical features, histology, or immunohistochemical profiles that accurately predict the behavior of this tumor. The utility of *EWSR1-CREB1* has demonstrated to be a valuable tool for the diagnosis of AFH. However, various morphological patterns and *EWSR1-CREB1* translocations have so far failed to be reliable prognostic indicators. Additional studies are needed to determine the possible impact of these features. We believe with this evidence, regardless of morphological appearance or molecular studies, AFH should not be underestimated, especially if the tumor is

in an area where complete wide local excision is not feasible. Therefore, one needs to be cognizant of metastatic potential in all AFH cases. It is our hope that this report raises awareness of what remains an unmet need in the knowledge of diagnosis and management of “angiomatoid fibrous histiocytoma with malignant features.” Hopefully, continued investigation drives further development of efficacious diagnosis and safe treatments for improving patient outcomes.

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References

1. Vicente-Dueñas C, Sánchez-García I. Angiomatoid fibrous histiocytoma (AFH). Atlas of Genet and Cytogenet in Oncol and Haematol. 2006; 10(2): 127-130.
2. Chen G, Folpe AL, Colby TV, Sittampalam K, Patey M, et al. Angiomatoid fibrous histiocytoma: unusual sites and unusual morphology. Modern Pathology. 2011; 24: 1560-1570.
3. Fanburg-Smith JC, Miettinen M. Angiomatoid “malignant” fibrous histiocytoma: A clinicopathologic study of 158 cases and further exploration of the myoid phenotype. Hum Pathol. 1999; 30(11): 1336-1343.
4. Thway K, Fisher C. Angiomatoid fibrous histiocytoma: the current status of pathology and genetics. Arch Pathol Lab Med. 2015; 139(5): 674-682.
5. Antonescu CR, Cin PD, Nafa K, Teot LA, Surti U, et al. *EWSR1-CREB1* is the predominant gene fusion in angiomatoid fibrous histiocytoma. Genes Chromosomes Cancer. 2007; 46(12): 1051-1060.
6. Enzinger F. Angiomatoid malignant fibrous histiocytoma: a distinct fibrohistiocytic tumor of children and young adults simulating a vascular neoplasm. Cancer. 1979; 44(6): 2147-2157.
7. Mitelman F, Johansson B, Mertens F. The impact of translocations and gene fusions on cancer causation. Nat Rev Cancer. 2007; 7(4): 233-245.
8. Hashimoto K, Nishimura S, Kakinoki R, Akagi M. Treatment of angiomatoid fibrous histiocytoma after unplanned excision: a case report. BMC Research Notes. 2018; 11: 628.
9. Hasegawa T, Seki K, Ono K, Hirohashi S. Angiomatoid (malignant) fibrous histiocytoma: A peculiar low-grade tumor showing immunophenotypic heterogeneity and ultrastructural variations. Pathology Int. 2000; 50(9): 731-738.
10. Hasegawa T, Hasegawa F, Hirose T, Sano T, Matsuno Y. Expression of smooth muscle markers in so called malignant fibrous histiocytomas. J Clin Pathol. 2003; 56(9): 666-671.
11. Rekhi B, Adamane S, Ghodke K, Desai S, Jambhekar NA. Angiomatoid fibrous histiocytoma: Clinicopathological spectrum of five cases, including *EWSR1-CREB1* positive result in a single case. Indian J of Pathol and Microbiol. 2016; 59(2): 148-152.
12. Rossi S, Suzhai K, Ijszenga M, Tanke HJ, Zanatta L. *EWSR1-CREB1* and *EWSR1-ATF1* fusion genes in angiomatoid fibrous histiocytoma. Clin Cancer Res. 2007; 13(24): 7322-7328.
13. Saito K, Kobayashi E, Yoshida A, Araki Y, Kubota D, et al. Angiomatoid fibrous histiocytoma: a series of seven cases including genetically



- confirmed aggressive cases and a literature review. *BMC Musculoskeletal Disorders*. 2017; 18: 31.
14. Chen Z, Yang Y, Chen R, Ng Ch, Shi H. Primary pulmonary myxoid sarcoma with *EWSR1-CREB1* fusion: a case report and review of literature. *Diagnostic Pathology*. 2020; 15: 15.
15. Thway K, Nicholson AG, Wallace WA, Al-Nafussi A, Pilling J, Fisher C. Endobronchial pulmonary angiomatoid fibrous histiocytoma: two cases with *EWSR1-CREB1* and *EWSR1-ATF1* Fusions. *Am J Surg Pathol*. 2012; 36(6): 883-888.
16. Costa MJ, Weiss SW. Angiomatoid malignant fibrous histiocytoma. A follow-up study of 108 cases with evaluation of possible histologic predictors of outcome. *Am J Surg Pathol*. 1990; 14(12): 1126-1132.
17. Maher OM, Prieto VG, Stewart J, Herzog CE. Characterization of metastatic angiomatoid fibrous histiocytoma. *J Pediatr Hematol Oncol*. 2015; 37(4): 268-271.
18. Costa MJ, McGlothlen L, Pierce M, Munn R, Vogt PJ. Angiomatoid features in fibrohistiocytic sarcomas. Immunohistochemical, ultrastructural, and clinical distinction from vascular neoplasms. *Arch Pathol Lab Med*. 1995; 119(11): 1065-1071.
19. Matsumura T, Yamaguchi T, Tochigi N, Wada T, Yamashita T, Hasegawa T. Angiomatoid fibrous histiocytoma including cases with pleomorphic features analysed by fluorescence in situ hybridisation. *J Clin Pathol* 2010; 63: 124-128.
20. Qian X, Hornick JL, Cibas ES, Dal Cin P, Domanski HA. Angiomatoid fibrous histiocytoma a series of five cytologic cases with literature review and emphasis on diagnostic pitfalls. *Diagn Cytopathol*. 2012; 40(2): 86-93.
21. Neto AA, Matthew-Thomas V, Monterroso C, Ibrahim O, Kachala S. Metastatic angiomatoid fibrous histiocytoma presenting as recurrent pneumothorax. *CHEST*. 2019; 156(4): 272-273.
22. Thway K, Stefanaki K, Papadakis V, Fischer C. Metastatic angiomatoid fibrous histiocytoma of the scalp, with *EWSR1-CREB1* gene fusions in primary tumor and nodal metastasis. *Hum Pathol*, 2013; 44(2): 289-293.
23. Shi H, Li H, Zhen T, Zhang F, Dong Y, et al. Clinicopathological features of angiomatoid fibrous histiocytoma: a series of 21 cases with variant morphology. *Int J Clin Exp Pathol* 2015; 8(1): 772-778.
24. Akiyama M, Yamaoka M, Mikami-Terao Y, Yokoi K, Inoue T, et al. Paraneoplastic syndrome of angiomatoid fibrous histiocytoma may be caused by *EWSR1-CREB1* fusion-induced excessive interleukin-6 production. *J Pediatr Hematol Oncol*. 2015; 37(7): 554-559.
25. Potter SL, Quintanilla NM, Johnston DK, Naik-Mathuria B, Venkatramani R. Therapeutic response of metastatic angiomatoid fibrous histiocytoma carrying *EWSR1-CREB1* fusion to the interleukin-6 receptor antibody tocilizumab. *Pediatr Blood Cancer*. 2018; 65(10): e27291.