Specific Comments To Authors: This case report describes a 13-year-old boy who was misdiagnosed for 6 months before being diagnosed with Angiomatoid Fibrous Histiocytoma (AFH), a rare tumor of the soft tissues. Diagnostic testing was inconclusive, and an excisional biopsy with gene rearrangement was necessary to confirm the diagnosis. The tumor was located in the submandibular area, which is a rare location for AFH. The report highlights the importance of specific gene testing in diagnosing AFH and determining its aggressiveness. The article is well written and reports a complete assessment of the case.

Answer:
I already put the files as you require and I'm looking forward to your answer! I'm also uploading below tables, figures and The Editing Certificate as you requested. I'm happy and open to all your suggestions. I hope the opinion will be positive for publication.

Difficulties in diagnosing angiomatoid fibrous histiocytoma of the head and neck region: A case report

Michcik A. et al. Diagnosing AFH

Abstract

BACKGROUND
Angiomatoid fibrous histiocytoma (AFH) is a rare, slow-growing soft tissue tumor. It is most common in children and young adults, which it appears mostly on the limbs and trunk in children and young adults. The biology of AFH remains unclear because of the small number of reported cases.
Diagnostic testing does not provide definitive results, therefore an excisional biopsy during surgery was made in order to diagnose the patient. A biopsy before surgery was not possible due to the localization of the lesion placed deep within the submandibular space. In addition, it has two clinical forms, that differ in terms of gene expression and clinical prognosis. It is important to inform the laboratory which specific gene testing is necessary. Here, we describe a case of rare AFH in the submandibular region using a full genetic panel, to use as there are two clinical forms of Angiomatoid Fibrous Histiocytoma AFH.

CASE SUMMARY
A 13-year-old boy who had been misdiagnosed in the past 6 months by his dentist visited our clinic because of a lesion in the submandibular area on the right side.

The lesion was homogeneous and painless upon palpation. No skin discoloration was observed.

Due to the non-specific radiological picture computed tomography (CT), magnetic resonance imaging (MRI), cone-beam computed tomography (CBCT), and ultrasound-guided biopsy were performed. A venous malformation was suspected on the MRI. None of the tests provided a definitive diagnosis. Owing to the non-specific radiological findings, the patient qualified for surgical treatment. The surgical procedure included an excisional biopsy. The diagnostic testing was extended using gene rearrangements. The most distinctive gene translocation in diagnosing AFH is within the EWS RNA-binding protein 1-CREB-binding protein (EWSR1-CREB). However, in this case, the diagnosis was confirmed by a rearrangement within the EWSR1 gene testing.

CONCLUSION

There have been cases reported of AFH in the head and neck in the past, but never specifically mentioned within the submandibular area. Therefore, this case will improve our knowledge of this tumor. AFH has no pathognomonic radiological features making it difficult to diagnose. Except surgical treatment specific gene (EWSR1, CREB) to test for should be a requirement and indispensable in diagnosing AFH. This will allow the determination whether it is an aggressive tumor or not.

AFH in the submandibular location is rare, and surgical treatment with genetic evaluation defines AFH type that affects subsequent procedures. Depending on the result, the presence of distant metastases should be excluded.

Key Words: Angiomatoid fibrous histiocytoma, Head and neck, Fine-needle aspiration, CREB-binding protein, Gene expression, Computed tomography

Core Tip: Angiomatoid fibrous histiocytoma (AFH) is a rare neoplasm of soft tissues with an atypical location and a large morphological spectrum, and is considered a lesion with diagnostic difficulties. In the case of AFH, diagnostics are crucial because they allow us to
plan further diagnostics and extend the treatment to distant tumors, in addition to local
treatment (in the case of metastases). Auxiliary diagnostic tests in the field of molecular
genetics (reverse transcription-polymerase chain reaction and fluorescence in situ
hybridization) are also important. The EWSR1-CREB1 t(2;22)(q33;q12) fusion assay is an
extremely important diagnostic element that should be routinely performed in patients with
AFH. In the case of gene translocations, we are obliged to increase the frequency of follow-
up examinations. Including chest imaging, apart from the standard head and neck
examinations. However, owing to the small number of clinical cases, it is difficult to predict
the course of the disease and assess patient prognosis. Publishing the results of AFH
treatment in patients with AFH will increase our knowledge of this tumor.

INTRODUCTION
Angiomatoid fibrous histiocytoma (AFH) is a rare, slow-growing, soft tissue tumor with a
low risk of malignancy[1]. It accounts for 0.3% of all soft tissue sarcomas. It was first described
in 1979 by Enzinger as "angiomatoid malignant fibrous histiocytoma" and it was classified
by the World Health Organization under the category of "tumors of uncertain differentiation"
in 2020. AFH is a lesion that rarely metastasizes[2-4]. It mostly occurs on the superficial
extremities of both children and young adults[3,5-7]. AFH It may can be misdiagnosed because
its clinical, histological, and radiological findings are similar to those of several tumors[5,8].
Here, we present the case of a young boy male with a lesion in the submandibular area on
the right side. This It is a rare location this lesion. In the available literature, AFH lesions have
been described in the upper and lower limbs but less often in the head and neck[9]. Because
of the rarity of AFH, we also performed a genetic test using the fluorescent in-situ
hybridization (FISH) method, which detected a rearrangement of the EWS RNA binding
protein 1 (EWSR1) gene. Diagnostic gene testing was extended to a specific test for the
translocation within the EWSR1-CREB-binding protein (CREB). No rearrangement was
observed within these genes in the present study.

Timeline
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<tr>
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<tr>
<td></td>
<td>standard contrast enhanced protocol</td>
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<tr>
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<tr>
<td></td>
<td>contrast with contrast injection protocol</td>
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<tr>
<td>October 2022</td>
<td>FNA fine-needle aspiration</td>
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<tr>
<td>November 2022</td>
<td>CBCT Cone Beam Computed Tomography</td>
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<td>November 2022</td>
<td>First operation surgical procedure</td>
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<tr>
<td>January 2023</td>
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<td>January 2023</td>
<td>Second operation surgical procedure</td>
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</table>

**CASE PRESENTATION**

**Chief complaints**

A 13-year-old boy was admitted to the hospital because of a lesion in the right submandibular area that had persisted for six months.

**History of present illness**

The patient was referred from a dentist, and was generally healthy and without allergies.
History of past illness
There was no obvious history of illness related to the disease.

Personal and family history
There was no significant personal or family history related to the disease.

Physical examination
Clinically, the lesion was firm, homogeneous, compact, painless to palpation, and 2.5 x 2 cm in size. No skin discoloration was observed. The boy did not complain of any sensory disorders and denied any growth changes.

Laboratory examinations
Routine blood test (November 2022) results were as follows: neutrophil cell count, 3.88 x 10^9/L (reference value: 2-7 x 10^9/L); neutrophil percentage: 58.6% (reference value: 40-74%).

Imaging examinations
The first radiological examination performed after the boy reported to the clinic was a computed tomography (CT) (Siemens Somatom Definition Flash; Siemens Healthcare, Germany) scan, which was performed on June 23, 2022. CT scans It showed a lesion under the mandible on the right side that has with smooth edges. It was not connected to the sublingual or submandibular glands.

Owing to the nonspecific CT image, magnetic resonance imaging (MRI) (1.5T MR Magnetom Aera Flash; Siemens Healthcare, Germany) with contrast (Gadovist, 5 mL) was performed on July 25, 2022. In the submandibular space on the right side, heterogeneous high signal intensity was observed on T2-weighted images, with a hemorrhagic component measuring 18 x 25 x 13 mm. The lesion adhered to the digastric muscle and the body of the mandible and involved the platysma (Figure 1, 2).
FURTHER DIAGNOSTIC WORK-UP

Histopathological diagnosis: irregular fibrohistiocytic hyperplasia with a variety of cells was observed between fibrous tissue, fatty tissue, and fibrous skeletal muscles. They were surrounded by multiple blood vessels. In addition, minor lymphocytes are rare in this circuit. Hyperplasia is an invasive and expandable condition. The phenotype of hyperplasia is as follows: SMA+, CD68+, CD163+, CD99+, desmine-, beta-catenin-, EMA-, CKAE1/AE3-, S100-, ALK-Bond-, CD34-, ERG-, and indeks Ki-67 IS 6% (Figure 6, 7). Figure 6: Diffuse expression of smooth muscle actin (SMA). Excision, magnification 400X.

Figure 7: Excision (400X, hematoxylin and eosin staining). Short spindled myoid and ovoid, histiocyte-like cells within a somewhat myxoid background.
FINAL DIAGNOSIS
The cumulative findings suggested fibrohistiocytic hyperplasia with an intermediate degree of malignancy, *angiomatoid fibrous histiocytoma (AFH).*

TREATMENT
The surgery was performed on November 29, 2022, under general anesthesia with oral intubation. A skin incision was made on the neck and the mass alone was removed, avoiding macroscopically unchanged tissues, which was considered the best solution. The affected external layer of the bone was exposed during the procedure. Along with the tumor, a bone sample was sent for histopathological examination. Surgical procedure No complications occurred (Figure 8 6, 9 7).

Figure 8 6 Intraoperative picture of submandibular. *Angiomatoid Fibrous Histiocytoma (AFH)*, tumor is marked with an arrow.
Figure 9 Intraoperative picture of a destroyed external layer of the mandible. It is marked with an arrow.

*Genetics research*

Because of the rarity of AFH, we also performed a genetic test using the FISH method – fluorescent in situ hybridization. The FISH test to check for the presence of the genetic translocation, that is, rearrangement gene EWSR1. Rearrangement gene EWSR1 was confirmed. The genetic study was conducted at the Laboratory of the Genetics Clinic of UCK in Gdansk. Pathomorphological and genetic studies validated the diagnosis of angiomatoid fibrous histiocytoma AFH.

As we know from previous research, the most aggressive form of AFH is associated with the involvement of both EWSR1 and CREB1 gene rearrangements. Tumors harboring these two genes exhibit recurrence and metastasis. Additional testing was performed to rule out the possibility that the tumor was aggressive.

*Results of Genetic Testing*
EDTA- and formalin-fixed, paraffin-embedded samples were submitted for testing. A total of 750 genes were tested, including CREB1, methylthioadenosine phosphorylase gene MTAP, tumor protein p53 TP53, and MRE11 gene (MRE 11).

The novel allele frequency, which is the frequency at which a mutated allele occurs in the sequencing data, was 100%. The observed frequencies are influenced by the tumor content and copy number alterations and do not directly correlate with the frequency of the variant in the tumor. Somatic alterations were classified according to their functional effect on protein levels into the following categories: inactivating/activating/function altered likely inactivating/activating/function altered unknown and benign.

The detected germline variant c.1867+5G>T; p.? in gene MRE11 is predicted to cause aberrant splicing and might therefore disrupt protein function. Based on the ACMG criteria, the variant was ranked as a variant of uncertain significance in the germline (Table 1, 2 3).

The variant 28/*28 detected in UDP-glucuronosyltransferase family 1 member A1 (UGT1A1) is a homozygous germline variant. For this genotype (also known as (TA)7/(TA)7rs8175347 or rs3064744), there is a possible increase in toxicity upon treatment with irinotecan-based chemotherapeutics. (Table 2 3).

No other genes or translocations, such as EWSR1-CREB, were found. This was related to a reduction in the scope of the control tests.

**Operative Technique**

We also followed-up with a new magnetic resonance imaging MRI with contrast (Gadovist, 5.5 mL) on January 3, 2023 (Figure 10).
Figure 10 MRI before second surgical procedure. Just below the outline of the body of the mandible, a lesion suspected of a residual tumor mass of $4 \times 8 \times 4$ mm is visible.

Based on histopathological examination results, a second surgery was conducted to completely remove the lesions with wide margins. The second surgery was performed on January 24, 2023, under general anesthesia with oral intubation. A skin incision was made within the scar from the initial surgery, and part of the platysma was removed, as well as part of the increased cohesion tissue located under the body of the mandible and surrounding lymph nodes. The specimen was sent for pathomorphological testing—histopathological examination. Intraoperative course was without complications. Intravenous pharmacotherapy administered after the first surgery was repeated (Figure 11).
Figure 11 Intraoperative view of the second procedure. No AFH irregularities were found. Tissue scar are marked with arrows.

OUTCOME AND FOLLOW-UP

Based on the results of the histopathological examination extended by genetic examination, the presence of an extremely rare soft-tissue sarcoma, angiomatoid fibrous histiocytoma AFH, was confirmed. To the best of our knowledge, this is the first reported case involving this location. Since gene translocation has not been demonstrated, particularly in EWSR1-CREB, surgery can be considered the main and final treatment and the AFH variant as non-aggressive. (Figure 12). The patient is currently reporting for routine check-ups at the Oral and Maxillofacial Surgery Clinic. Locally, there were no signs of recurrence.
**DISCUSSION**

AFH, first discovered in 1979 by Enzinger, is a very rare soft tissue tumor with a relatively good prognosis and medium malignancy potential\[10,11\]. It accounts for 0.3% of all soft tissue sarcomas. It is considered an intermediate tumor. In the past, it was classified as a malignant variant, but owing to its course and treatment, it was found to have a favorable prognosis\[12\]. It occurs most often in the deep dermis and subcutaneous tissues of the upper and lower limbs\[6\]. It mainly affects children and young adults, and there have been a few reported cases involving older adults\[12\]. The tumor growth is slow and painless. Patients are often unaware of this disease\[2\]. This may be accompanied by fever and general weakness. However, this criterion does not define a unit\[11\].

Based on the case presented above, diagnosis is difficult and yields ambiguous results. From the clinical and radiological perspectives, lymphatic malformations, lymphovenous malformations, bone aneurysmal cysts, hematomas, hemangiomas, and lipomas can be suspected\[5\]. Radiological methods for AFH are not specific, and do not lead to a specific diagnosis.

Surgical treatment alone enabled us to obtain additional information. Based on the available literature, surgery involving the removal of a lesion with a wide margin of macroscopically unchanged tissue is the best solution. In the head and neck area, performing a wide excision is often clinically impossible and is associated with disease recurrence in the future. However, local recurrence of the lesion depends on the size and depth of tissue infiltration\[11\] and local recurrence occurs in 15% \[13\] or, according to another source, in 2-12% of cases\[5\].

Based on immunohistochemistry results, CD68, CD99, EMA, and wimentyne (EP21) were positive for epithelial membrane antigens, whereas cytokeratin and S100 protein were negative\[5,11,12\]. However, desmine was positive and negative in two different assays\[2,5,12\].

Because the diagnosis of AFH can be difficult owing to variable histological features and the lack of highly sensitive immunohistochemical markers, the immunohistochemical markers TLE1 and BCOR have been tested and proven useful. The sensitivity and specificity
of TLE1 marker for detecting AFH were 100% and 94.4%, respectively. Therefore, TLE1 can be considered as a highly sensitive immunohistochemical marker[14].

In addition, FISH tests can detect gene rearrangements. The three most characteristic AFH translocations are: EWSR-CREB1 t(2;22)(q33;q12), EWSR1-ATF1 t(12;22)(q13;q12), and FUS-ATF1 t(12;16)(q13;p11)[5,15,11,16-18]. The most common translocation is EWSR-CREB1 (90%)[19,20]. This is associated with the risk of distant metastases. Therefore, we decided to keep the patient under observation and scheduled follow-up visits. Distant metastases occur in 5% of cases and are mainly located in the regional lymph nodes or lungs[13]. The EWSR1-CREB fusion is also found in gastrointestinal clear cell sarcoma (CCSLGT) and primary myxoid lung sarcoma (PPMS)[19]. CCSGT is a rare cancer that occurs in the walls of the small intestine, mainly in young adults and is similar to AFH. In contrast, PPMS is a rare lung cancer that arises intrabronchial[19].

The histology of AFH consists of a multinodular growth of spindle-shaped cells. These cells have a characteristic syncytial appearance. The pseudovascular spaces are filled with cancer cells and blood. Histologically, a thick, fibrous pseudocapsule with deposited hemosiderin together with lymphoplasmacytic cuffs can also be distinguished[21]. Regarding the morphology, AFH showed a wide spectrum. Multinodular cell growth was consistent. A specific feature of the morphology is the presence of small, clear cells with scanty cytoplasm. This resembles Ewing's Sarcoma[21].

Ultrasonography is the least invasive radiological examination. The image shows a heterogeneous hypoechoic structure that may contain cystic spaces or fluid levels[6,19]. On computed tomography (CT), AFH is described as a heterogeneous soft tissue lesion with hyperdense areas suggestive of hemorrhage and hypotensive areas that could indicate necrosis or a cystic/myxoid lesion[6]. MRI may show hypointense pseudocapsules (double-rim sign), cystic changes, peritumoral edema, and fluid-fluid levels. On T1-weighted images, the lesion is most often isotensive to the muscles, whereas on T2-weighted images, it is heterogeneously hyperintense[6,19,21,22].

Treatment is surgical in most cases. Favorable prognosis has been established for patients with AFH after treatment. As mentioned above, local recurrence occurs in up to 15% of cases, whereas distant metastases occur in < 5% of cases. The presence of gene translocations, especially EWSR1-CREB, is also important because of the increased risk of
distant metastases. In the current literature, Patients with distant metastases have been treated with systemic chemotherapy; however, no benefits have been reported. AFH has an unspecified course that is rarely predictable[21].

CONCLUSIONS

Angiomatoid fibrous histiocytoma (AFH) is a rare neoplasm of soft tissues with an atypical location and a large morphological spectrum, and is considered a lesion with diagnostic difficulties. In the case of AFH, diagnostics are crucial because they allow us to plan further diagnostics and extend the treatment to distant tumors, in addition to local treatment (in the case of metastases). Auxiliary diagnostic tests in the field of molecular genetics (reverse transcription polymerase chain reaction or FISH) are also important.

The EWSR1-CREBI t(2;22)(q33;q12) fusion assay is an extremely important diagnostic element that should be routinely performed in patients with AFH. In the case of gene translocation, we are obliged to increase the frequency of follow-up examinations, including, apart from standard examinations of the head and neck, chest CT imaging.

However, owing to the small number of clinical cases, it is difficult to clearly predict the course of the disease and assess the prognosis of patients. Publishing the treatment results for patients with AFH will deepen our knowledge about this tumor.

ACKNOWLEDGEMENTS

Words of thanks to Bień M and Wojciechowska B who have made genuine contributions to the manuscript.

REFERENCES


19 Colangeli M, Rimondi E, Spinnato P, Donati DM, Manfrini M. Difficult diagnosis of Angiomatoid Fibrous Histiocytoma of the leg mimicking a benign condition. *Journal of*


Footnotes

**Informed consent statement:**

Written informed consent was obtained from the patient for the publication of this case report.

**Conflict-of-interest statement:**

All the authors report no relevant conflicts of interest for this article.
Figure Legends

Figure 1 Focal change on the right side of the submandibular space initially diagnosed as a venous malformation.

Figure 2 Visible irregular outline of a moderately hyperintense area of 18 × 25 × 13 mm.

Figure 3 Fine Needle Aspiration FNA at high magnification (400X, hematoxylin and eosin staining). Single bland cell with oval nucleus, smooth nuclear membranes, and conspicuous nucleolus.

Figure 4 Fine Needle Aspiration FNA at high magnification (400X, hematoxylin and eosin staining). Spindle bland cells within an eosinophilic background.

Figure 5 A smooth contoured 3 mm defect in the cortical layer of the inner mandible on the right side near the border of the scan.

Figure 6 Diffuse expression of smooth muscle actin (SMA). Excision, magnification 400X.

Figure 7 Excision (400X, hematoxylin and eosin staining). Short spindled myoid and ovoid, histiocyte-like cells within a somewhat myxoid background.

Figure 8 Intraoperative picture of submandibular. Angiomatoid Fibrous Histiocytoma (AFH), tumor is marked with an arrow.

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Figure 11 Intraoperative view of the second procedure. No AFH irregularities were found. Tissue scar are marked with arrows.

Figure 12 Proposed diagnostic and therapeutic path.
Table 1. Variant with potential therapeutic relevance of gene MRE11 (MRE11). MTB- Molecular Tumor Boards. EMA- European Medicines Agency. FDA- Food and Drug Administration. PARP inhibitor- inhibitor of the enzyme poly ADP ribose polymerase.

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<th>Gene</th>
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<th>Effect on protein function</th>
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Table 2. Relevant therapeutics for gene MRE11. **BRCA1**- Breast cancer type 1 susceptibility protein. **BRCA2**- Breast cancer type 2 susceptibility protein. **HRD**- cancer associated with Homologous Recombination Deficiency.

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Table 2-3. Variants with pharmacogenetic relevance gene UDP glucuronosyltransferase family 1 member A1 (UGT1A1).

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