Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2022.02.2.022

December 2022
Volume 2
Issue 2

Myxoid Angiomatoid Fibrous Histiocytoma: Report of An Uncommon Neoplasm with a Review of Literature

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Received on, 09 September 2022 - Accepted on, 24 September 2022 - Published on, 25 October 2022

Abstract:

Angiomatoid Fibrous Histiocytoma (AFH) is a rare soft tissue tumor usually seen in the extremities of children and adolescents. Classically AFH presents as a painless cystic mass that shows blood filled spaces on cut section and bland histiocyte-like cells on microscopic examination. Predominance of myxoid stroma is a rare finding in AFH, usually seen with other classical features. Herein, the reseachers report a case of myxoid AFH with both unusual clinical presentation and uncommon histopathological features with a review of literature.

Key words: *Myxoid, Angiomatoid fibrous histiocytoma.*

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Case report

An 11-year-old male child presented by a painful thigh mass that had been noted for 7 months. MRI showed a deeply seated thigh mass measuring 7cm in maximum dimension not related to the underlying bone or the overlying skin. Surgical resection of the mass was done and showed a well-circumscribed solid firm mass having a whitish yellow cut section [Figure 1].

Fig. 1. A well circumscribed mass having a yellowish white tan cut surface.

Microscopically the mass was well circumscribed, lobulated composed predominantly of hypocellular areas and less frequently hypercellular zones surrounded by a rim of lymphoid tissue showing germinal centers [Figure 2]. The hypocellular areas showed myxoid basophilic stroma with oval to rounded cells having little pleomorphism and arranged in a reticular pattern. Some vacuolated cells were noted in these myxoid areas. Rare pseudovascular spaces filled with blood were observed. Scattered vessels were noted, most of which are slender and curvilinear. The hypercellular areas showed bland spindled cells arranged in fascicles with scant mitotic figures, but without abnormal forms. Collagen bundles were focally noted in some areas among loosely arranged spindled cells. Focal herringbone pattern was noted [Figure 3]. No necrosis was seen.

A panel of immunohistochemical antibodies (IHC) including desmin, smooth muscle actin (SMA), epithelial membrane antigen (EMA), S100 and MUC4 was done. Tumor cells showed diffuse strong cytoplasmic staining for desmin, focal staining for both smooth muscle actin (SMA) and epithelial membrane antigen (EMA), whereas they were negative for S100 and MUC4 [Figure 4]. So a diagnosis of myxoid variant of angiomatoid fibrous histiocytoma was made.

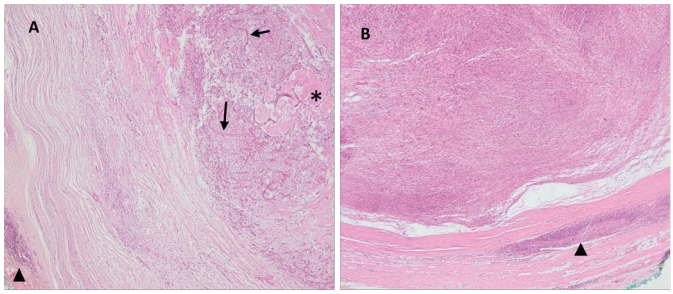

Fig. 2. A: A well circumscribed predominantly myxoid stoma-rich tumor composed of loose areas showing slender blood vessels (arrows) and cystic areas filled with myxoid material (asterisk). B: Hypercellular spindled areas were noted. The growth was surrounded by a rim of lymphoid tissue (arrowheads). H&E x10.

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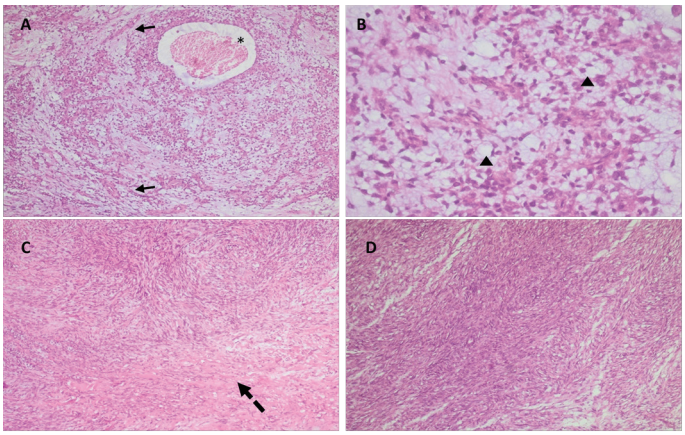

Fig. 3. A: The hypocellular areas showed loose myxoid areas with slender curvilinear blood vessels (arrows) and an occasional pseudovascular space (asterisk). H&E x10. B: The cells were small round to oval arranged in a reticulated pattern. Few vacuolated cells were noted (arrowheads). H&E x400. C: The hypercellular areas showed bland spindle cells with collagen bundles (dotted arrow). D: Herringbone pattern was noted. H&E x100.

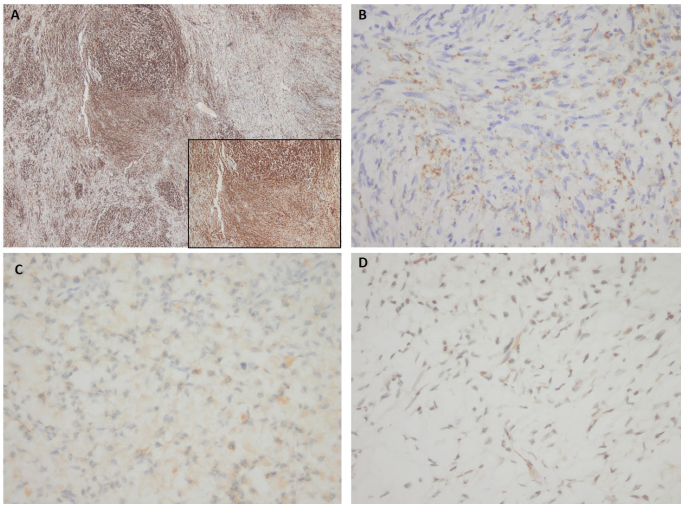

Fig. 4. A: Positive staining for desmin in hypocellular areas (x100) Inset: High power showing diffuse staining for desmin in hypercellular areas. B: Focal weak staining for CD68. C: Focal moderate staining for EMA. D: Focal moderate staining for SMA. (x400).

Discussion

Angiomatoid Fibrous Histiocytoma (AFH) is an uncommon soft tissue tumor representing 0.3% of all soft tissue neoplasms. It is a tumor of an uncertain type and an intermediate malignant potential [1]. It was previously referred to as 'angiomatoid malignant fibrous histiocytoma'; a term depicting its resemblance to vascular neoplasms and its potentially aggressive behavior [2].

AFH is seen mainly in children and adolescents. It usually arises on the extremities in the subcutaneous tissue as a nodular mass often with cystic areas. It shows a slow rate of growth [3]. Contrary to the present case, pain is not a common presenting symptom for this tumor; however, the secretion of cytokines – particularly IL-6 – can lead to systemic manifestations such as fever, anemia and weight loss. This has been attributed to binding of the IL-6 promotor region to the fusion protein EWSR1-CREB [4].

Classically, these tumors are well-demarcated masses of few centimeters in maximal dimension having a tan to brown cut section with grossly appreciable cystic spaces filled with blood. Microscopically, AFH shows central cystic hemorrhagic areas admixed with a uniform population of histiocyte-like cells surrounded by a dense peripheral rim of lymphoid tissue enclosed in a thick fibrous pseudocapsule. The lesional cells show a pale eosinophilic cytoplasm with bland round to oval nuclei showing no atypical features [5]. However, in rare instances severe atypia, multinucleation and hyperchromasia are encountered with no significant effect on the clinical outcome [6].

Cystic hemorrhagic areas are a diagnostic feature of AFH and have granted these tumors their name. They often lead to an erroneous diagnosis of a vascular tumor, however – unlike true vascular spaces – these pseudovascular spaces lack an endothelial lining. Small vessels can be seen in the vicinity of tumor nodules, though are often not a prominent feature. Hemosiderin deposition and fibrous tissue can be very prominent especially in longstanding tumors [5]. However, in a review of the spectrum of histological features in a series of 27 cases of AFH, the presence of pseudovascular spaces was observed in only 11 cases (43%) [7]. In another series of 13 cases from Taiwan, four cases had solid growth pattern, and did not show pseudovascular spaces [8]. The current case showed only a few occasional pseudovascular spaces.

Lymphoid tissue – a characteristic feature of AFH- can be admixed with plasma cells and eosinophils [7] but is more often in the form of lymphoid aggregates sometimes showing germinal centers – as seen in the present case. The presence of lymphoid follicles with germinal centers can lead to the initial consideration of lymph node metastasis. However, the lack of sinuses and the haphazard distribution of germinal centers not limited to subcapsular region stand against a nodal lesion [5].

Uncommon features of AFH include small cell change, alveolar pattern, predominantly myxoid areas and spindle cell pattern [5, 9, 10]. The predominance of these rare features can often be very misleading and direct the pathologist's attention to other lesions as round cell sarcomas particularly Ewing sarcoma, alveolar rhabdomyosarcoma, myxoid-rich tumors and spindle cell sarcomas [5].

Since AFH is a tumor of uncertain differentiation, the IHC features of these lesions can be very confusing and inconsistent. Despite the fact that histiocyte-like cells

predominate in these tumors, only half of the cases express CD68, a percentage surprisingly similar to the expression of CD99, desmin and EMA in AFH [11, 12]. Other less commonly expressed markers include ALK and other muscle markers as calponin and SMA [12, 13].

Multiple translocations with resultant fusion proteins were reported in AFH the most common of which is EWSR1-CREB1, followed by EWSR1-ATF1 and FUS-ATF1 being the least common [14, 15, 16]. None of these fusions appear to be associated with specific clinical or pathological features [5]. Of note, EWSR1-CREB1 and EWSR1-ATF1 are not unique to AFH and can be encountered in other tumors particularly clear cell sarcoma of the soft parts [17].

Myxoid AFH represents less than 5% of all cases of AFH. Myxoid stroma is expected to represent at least 60% of the tumor to be included in the myxoid AFH category [9]. The largest series of these tumors was reported in 2014 by Schaefer et al. [9] followed by few reports of similar findings [18, 19]. It has recently been reported in uncommon sites including the intracranial location [20]. Apart from the predominance of myxoid stroma, the histological, immunohistochemical and cytogenetic features of this variant is similar to those of the classic AFH. However, not all tested cases for EWSR1 and FUS genes by Schaefer et al. showed rearrangement in myxoid AFH challenging their diagnostic utility [9]. Intracranial tumors show a unique fusion between EWSR1-CREM – a gene belonging to the CREB family [20].

The present case showed a constellation of rare histological features. The predominance of curvilinear slender vessels with only a very few pseudovascular spaces were seen. No hemosiderin pigment was observed. The complete absence of the classic histiocyte-like cells with the stark predominance of myxoid areas occupying more than 80% of the tumor along with the herringbone like spindled areas; all posed a diagnostic challenge. Only the fibrous pseudocapsule and the peripheral lymphoid follicles gave the initial clue to the possibility of myxoid AFH, however, other myxoid-rich lesions were initially considered; particularly low grade fibromyxoid sarcoma, neurogenic benign tumors, extraskeletal myxoid chondrosarcoma and myxoid liposarcoma.

In accordance with the literature, the present case showed strong desmin expression but weaker EMA and SMA. Only scattered cells were positive for CD99. The absence of histiocyte-like cells characteristic of this lesion came in agreement with the weak and focal CD68 expression. Positivity for desmin and EMA excluded the prospects of extraskeletal myxoid chondrosarcoma and myxoid liposarcoma. MUC4 and S100 negativity excluded the diagnosis of low grade fibromyxoid sarcoma and neurogenic tumors, respectively. Negativity for S100 also excluded myoepithelial tumors that can show some degree of similarity to myxoid AFH.

As previously mentioned, AFH was initially thought to be an aggressive tumor [2]. However, follow-up of large series showed that local recurrence does not exceed 12 % of cases and is mostly related to incomplete excision and that distant metastasis is seen around 5% of cases [6, 12]. Therefore, in the recent classifications of soft tissue tumors the "malignant" designation was removed from the name of these lesions [1]. Only surgical resection with negative resection margins is curative for these lesions [5].

Conclusion

AFH can present as a painful solid mass. Some of the classic features of these lesions may be very focal – as the blood-filled-cystic spaces – while others can be completely absent – as the histiocyte-like cells. In these cases, identification of even few cystic spaces filled with blood, along with other classical features on histopathological examination can be a clue to the diagnosis. The integration of clinical data with gross and microscopic features is mandatory in such challenging cases to reach an accurate diagnosis.

Conflicts of interest

The authors have no conflicts of interest to declare.

Funding

The present work received no specific grants.

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Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2022.02.2.022

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