# Content

## Solid Variant of Angiomatoid Fibrous Histiocytoma Masked by Interstitial Granuloma Annulare in a 13-year-old Child: No Evidence for Translocation Breakpoints

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Angiomatoid fibrous histiocytoma (AFH) is a very rare tumour entity, which predominantly affects adolescents and young adults with a slight female predilection (1–3). As the tumour often appears as a non-characteristic, skin-coloured, slowly growing nodule, mostly on the extremities, the recognition of AFH can be challenging and may require sophisticated diagnostic techniques including immunohistochemistry and molecular genetic analysis. Here, we present a child with a long-standing solitary nodule on the right thigh, which was initially misdiagnosed as interstitial granuloma annulare (GA). The correct diagnosis of solid variant of AFH could only be established after complete excision of the nodule.

### CASE REPORT

A 13-year-old girl presented with a 16-months history of a solitary, asymptomatic, slowly growing skin-coloured nodule, measuring 1 × 1.5 cm in size located on the ventral aspect of her left lower thigh (Fig. 1A). Nine months ago, a punch biopsy suggested interstitial GA. Various topical treatments including glucocorticoids, pimecrolimus and anthralin were applied but led to no improvement. A suspect echolucent subcutaneous mass detected by high resolution ultrasound prompted the complete excision of the nodule (Fig. 1A).

Histology showed interstitial infiltrates with CD68$^+$ histiocytes within the upper and mid dermis, compatible with interstitial GA (Fig. 1B). However, histological investigation of the lower dermis and subcutis revealed a well-circumscribed tumour consisting of multiple nodules comprised of atypic spindle and epithelioid cells with a marked nuclear pleomorphism (Fig. 1C, D). The tumour cells were surrounded by an inflammatory infiltrate composed of plasma cells and small lymphocytes arranged as secondary lymph follicles with prominent germinal centres. The nodule was enclosed by a dense fibrous pseudo-capsule (Fig. 1C). Immunostaining showed a strong cytoplasmic positivity for Vimentin, a multifocal positivity for Desmin as well as focal expression of SMA, while EMA was negative, consistent with a solid variant of angiomatoid fibrous histiocytoma (Vimentin$^+$, Desmin$^{+/-}$, sm-Actin$^{+/-}$, CD20$^-$, CD23$^-$, CD43$^-$, CD3$^-$, CD4$^-$, CD56$^-$, CD30$^-$, CD123$^-$, TCL1$^-$, MNF116$^-$, KL1$^-$, EMA$^-$, S-100$^-$, HMB45$^-$, MelanA$^-$, MIC2$^-$, Calretinin$^-$, AE1/AE3$^-$, Caldesmon$^-$, MyoD1$^-$, Myf-4$^-$, CD34$^-$, CD68$^-$, CD45RA$^-$, Ki-67 2%).

Recently, recurrent chromosomal breakpoints in the *EWSR1* locus (22q12) and the *FUS* locus (16p11) leading to a *EWSR1/CREB1* (t(2;22)(q33;q12)), a *EWSR1/ATF1* (t(12;22)(q13;q12)) or a *FUS/ATF1* (t(12;16)(q13;p11)) gene fusion have been identified in AFH (3). To determine the presence of these chromosomal translocations, we performed interphase fluorescence in situ hybridization (FISH) on lesional skin targeting the *EWSR1* (22q12) and the *FUS* (16p11) locus (all probes from Abbott/Vysis). Evaluation of 200 nuclei showed no evidence for breakpoints affecting these regions (Fig. 1D, Table SI; avialable from http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1698).

Staging procedures, including computed tomography scans and an ultrasound of the peripheral lymph nodes revealed an enlarged lymph node within the right groin as well as a solitary pulmonary nodule (3.4 mm diameter). Since this pulmonary nodule proved stable in a CT-control after 3 months, it was considered benign. An inguinal lymph node biopsy revealed a dermopathic lymphadenopathy with no evidence of infiltrating tumour cells. Re-excision of the area on the left lower thigh with a margin of 1 cm was performed and no tumour relapse has been observed to date.

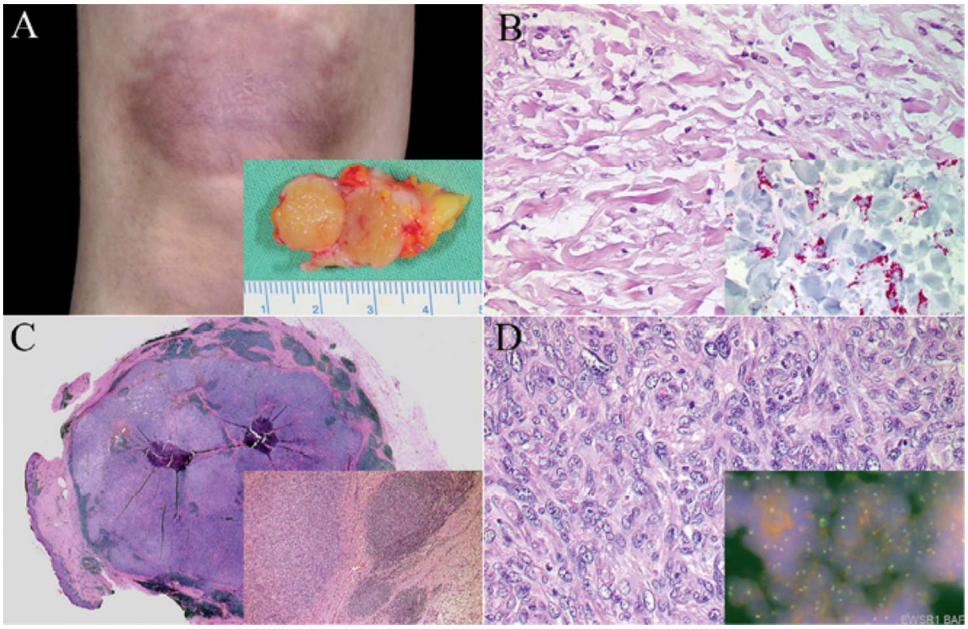


*Fig. 1.* (A) Clinical picture of Angiomatoid fibrous histiocytoma (AFH) with cutaneous hyperpigmentation induced by anthralin therapy. Inset: Subcutaneous nodule of AFH. (B) Histology of interstitial granuloma annulare showing infiltrates of histiocytes in the upper and mid dermis (H&E). *Inset*: Interstitial infiltrates of histiocytes highlighted by CD68 immunostaining. (C) Low power photomicrography showing nodular configuration of tumour cells surrounded by inflammatory infiltrates (H&E). Inset: Lymphoid infiltrates forming germinal centres separated by a fibrous pseudo capsule. (D) The tumour consisted of spindle and epithelioid atypic cells with significant nuclear pleomorphism. Inset: Fluorescence *in situ* hybridization. Interphase nuclei hybridised with LSI *EWSR1* probe (Dual Color, Break Apart Rearrangement Probe; Vysis). The colocalisations of the red and green signals excluded the presence of a translocation affecting the *EWSR1* gene.

## DISCUSSION

AFH was initially described by Enzinger in 1979 (4). Wide local excision has been proposed as the treatment of choice for AFH (3). As sporadic cases of metastases (< 5%) and local recurrences (up to 15%) have been reported, it is important to distinguish this entity from benign processes (2, 5). On the other hand, it is necessary to exclude malignant fibrous histiocytoma and other highly malignant tumours to avoid overtreatment (6). To our knowledge this is the first case of AFH masked by an overlying interstitial GA.

Systemic symptoms such as anaemia, pyrexia and malaise have been reported in association with AFH suggesting cytokine production by the tumoural tissue (1, 4, 5). Since our patient suffered from mild anaemia at the time of diagnosis and induction of interstitial GA by immunomodulatory drugs like interferon-α has been described, one may speculate that in our case the interstitial GA was induced by AFH-derived cytokines (7). It is noteworthy that the existence of the malignant tumour was initially missed due to the too superficial biopsy. Palpation of the subsurface tumour and ultrasound scan must, therefore, lead to a deeper skin biopsy.

Histologically, AFH is characterised by the proliferation of round or spindled cells interrupted by areas of haemorrhage, a surrounding inflammatory infiltrate often forming germinal centres and a fibrous pseudocapsule (1, 2, 4, 5). If blood filled spaces are present, the spectrum of histologic differential diagnoses comprises vascular tumours such as spindle cell haemangioma, cutaneous angiosarcoma or nodular Kaposi sarcoma as well as aneurysmal benign fibrous histiocytoma (3). However, up to 18–50% of AFH lack these blood filled spaces and stromal haemorrhage resulting in diagnostic challenges (2, 5). Given that the majority of AFH express Desmin, rhabdomyosarcoma has to be excluded and CD99 positivity can lead to misdiagnosis of Ewing sarcoma or primitive neuroectodermal tumours (2).

Recent cytogenetic studies have identified three recurrent translocations in AFH, a t(2;22)(q33;q12) resulting in a *EWSR1/CREB1* fusion, a t(12;22)(q13;q12) resulting in a *EWSR1/ATF1* fusion and a t(12;16)(q13;p11) resulting in a *FUS/ATF1* fusion (8–10). While 76–93% of AFH harbour *EWSR1* rearrangements on 22q12, chromosomal breakpoints affecting the *FUS* gene on 16p11 are much rarer (about 7%) (11, 12). In our case, *EWSR1* and *FUS* breakpoints could not be detected by FISH analysis. While the *EWSR1* gene acts as a repressor in normal tissue, the translocated *EWSR1* can play a role in the tumourigenic process via deregulation or aberrant activation of the fusion protein target (13). Recently, it was found that *CREB1* is required for *VEGF*-induced *Nurr1* expression which mediates tumour angiogenesis (14). However, it is completely unclear, if altered CREB1 expression could contribute to formation of the blood filled spaces in AFH.

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