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# Multinucleated cell angiohistiocytoma: A case report and literature review

Ahmed Shah, Samih Salama, Gabriella Gohla, Salem Alowami

## ABSTRACT

**Introduction:** Multinucleate cell angiohistiocytoma (MCAH) is a rare vascular and fibrohistiocytic tumor of the skin with characteristic component of multinucleated giant cells. Herein, we discuss the case with clinicopathologic correlation of MCAH with two rare cutaneous tumors containing multinucleated giant cells: giant cell fibroblastoma (GCF) and dermatofibroma with monster cells (DFMC). Clinical and histopathological characteristics of these three lesions have not been compared before. It is our aim to help highlight the key differences that will help pathologists differentiate between MCAH, DFMC, and GCFB. **Case Report:** We report a case of a 68-year-old woman with a skin lesion from her thigh, which was initially thought to represent a dermatofibroma with monster cells (DFMC), but was subsequently diagnosed as MCAH. **Conclusion:** Multinucleate cell angiohistiocytoma, DFMC, and GCF have several overlapping clinical and immunohistochemical characteristics. Therefore, clinical presentation cannot be solely relied upon to differentiate MCAH from DFMC. The diagnosis should be made after considering their histological characteristics supplemented by clinical presentation and immunohistochemical differences.

**Keywords:** Dermatofibroma, Giant cell fibroblastoma, Multinucleate cell angiohistiocytoma

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## INTRODUCTION

Multinucleate cell angiohistiocytoma (MCAH) is a rare vascular and fibrohistiocytic tumor characterized by proliferation of vessels and multinucleated stromal cells amid thickened collagen bundles [1]. It was first clinically described in 1985 by Smith and Jones presenting as reddish-purple nodules affecting mostly the face and distal extremities of middle-aged women [2]. Clinically, MCAH has a broad differential diagnosis including but not limited to dermatofibromas, microvenular hemangioma, lichen planus, granuloma annulare, sarcoid, eruptive leiomyoma, lymphomatoid papulosis, papulonecrotic tuberculid, Kaposi sarcoma, and leukemia and lymphoma with cutaneous involvement [2, 3].

Although its pathogenesis remains elusive, MCAH is considered by most studies to be a benign entity. Interestingly, MCAH has shown spontaneous resolution, and in one case within nine months after initial presentation [3]. The spontaneous resolution of some cases, ultrastructural studies showing fibrohistiocytic features, and its association with other inflammatory processes such as Hidradenitis suppurativa suggests a reactive etiology [4]. However, some authors consider MCAH a variant of dermatofibroma, that has evidence of it having both a reactive and neoplastic pathogenesis [5].

Clinically, MCAH presents as solitary, multiple, grouped, or generalized reddish-purple papules and nodules that are usually located in dorsal hands and

lower extremities [2, 6]. Solitary lesions of MCAH, as in our case, have 3 times greater incidence in females than males, whereas, generalized forms have an equal incidence [2]. The sizes of the lesions' vary between 2 and 15 mm in diameter [6]. There are no reported recurrences and the lesion often spontaneously regresses without treatment, supporting an inflammatory etiology of the lesion [4, 7].

Histologically, MCAH is characterized by proliferation of dermal vasculature associated with spindle cells, multinucleated cells amid thickened collagen bundles, hypercellularity of dermal interstitium, and mixed inflammatory infiltrate and notable perivascular inflammation [1].

The histological differential diagnoses for MCAH includes dermatofibroma with monster cells (DFMC), or atypical fibrous histiocytoma, and giant cell fibroblastoma (GCF) which are cutaneous lesions that also contain multinucleated giant cells. All these lesions have different prognostic implications. Therefore, differentiating between these three rare entities by comparing and contrasting clinical, histologic and immunohistochemical features has clinical significance for patient management and monitoring.

## CASE REPORT

Our case is a 68-year-old woman who presented with a right thigh skin lesion. Her past medical history was only significant for gastroesophageal reflux disease, which was treated with Nexium. The patient had no history of endocrinopathies, autoimmune diseases, malignancies, or inflammatory dermatoses. The patient was not taking any other medications. Clinically, the lesion was described as raised, reddish-brown papule measuring 0.6 × 0.6 × 0.2 cm. This lesion progressively became larger over several months, and had a history of rubbing, trauma, and bleeding to the area prior to the tumor development. Based on the history of trauma and its clinical appearance, it was diagnosed as dermatofibroma. A biopsy was obtained, and it was histologically diagnosed as DFMC. In order to exclude the possibility of DFSP, an excision of the tumor was performed and the specimen was sent for dermatopathology consultation. Histologically, the tumor was composed of thickened collagen bundles, interstitial hypercellularity, and proliferation of haphazardly arranged capillaries and small venules, along with bizarre, and often stellate-shaped multinucleated giant cells in the dermis (Figure 1A–C). Immunohistochemically, the stromal cells and multinucleated cells showed positivity for Factor XIIIa, and endothelial cells were positive for CD34, whereas they were all S100 negative (Figure 1D and E). The histology and immunohistochemistry were consistent with the final diagnosis of MCAH. The patient was informed by clinician that the lesion was benign and was discharged from care.

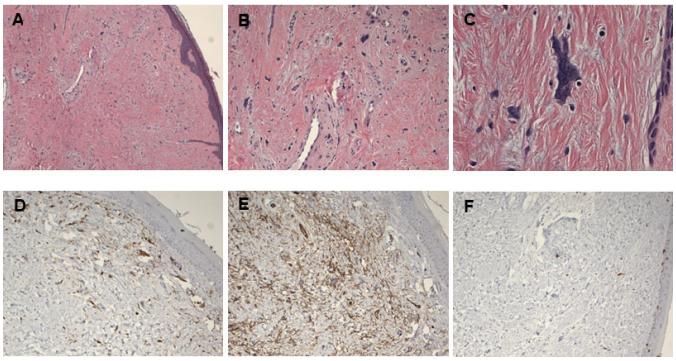


Figure 1: Representative morphological images and immunohistochemistry of multinucleate cell angiohistiocytoma. (A) The blood vessels, giant cells, and spindle cell stroma (H&E staining, ×100 magnification). (B) The blood vessels, giant cells, and spindle cell stroma (H&E staining, ×200 magnification). (C) Multinucleated giant cells (H&E staining, ×400 magnification). (D) Tumor cells positive for fibrohistiocytic marker Factor XIIIa (×100 magnification). (E) Tumor cells positive for endothelial marker CD34 (×100 magnification). (F) Tumor cells negative for S100 (×100 magnification).

## DISCUSSION

Our case highlights the difficulty experienced by practicing pathologists in differentiating MCAH from other rare cutaneous entities with similar histology like DFMC and GCF. However, MCAH, GCF, and DFMC can be distinguished by combination of their clinical histological and immunohistochemical characteristics.

Like MCAH, DFMC and GCF are cutaneous lesions that also contain multinucleated giant cells. Giant cell fibroblastoma is a low-grade, slowly progressive dermal or subcutaneous spindle cell neoplasm that usually affects males of pediatric population mostly in the back and thighs [1]. The lesion size ranges from 1 to 8 cm [8], and usually affects boys at median age of 6.5 (Table 1) [9]. Although GCF is primarily a pediatric lesion, cases affecting older individuals have been noted [10]. Giant cell fibroblastoma shares molecular etiology with dermatofibrosarcoma protuberans (DFSP) involving chromosome 17 and 23 translocation resulting in the fusion of collagen gene (COL1A1) with platelet-derived growth factor β (PDGFβ) gene [11]. Unlike MCAH, GCF has a significant rate recurrence after excision, but there are no reported metastases or deaths from the tumor (Table 1) [11]. Post-excision recurrences of GCF are reported in approximately 50% of lesions within 7 years [11]. Moreover, frequent reports have been made of GCFs recurring as DFSP in adults [12].

In contrast, DFMC is a tumor that occurs usually in middle age adults. It clinically presents as a solitary, well-circumscribed to poorly defined nodules ranging from 0.3–4 cm in size [13]. Although DFMC mostly occurs in the trunk and extremities, it also occurs in the neck and genitals, and has an equal male-to-female incidence (Table 1) [13]. It shares architectural features of dermatofibroma (DF) but with additional features of

large atypical and bizarre giant cells with hyperchromatic dual or multiple nuclei [13]. Although DFMC is usually considered benign, it shows up to 14% post-excision recurrence rate, 5 reported metastases including 1 death [13, 15].

Histologically, MCAH is characterized by benign proliferation of dermal vasculature associated with spindle cells, bizarre basophilic multinucleated cells amid thickened collagen bundles, hypercellularity of dermal interstitium, and mixed inflammatory infiltrate

Table 1: Clinicopathologic comparison of MCAH, GCF, and DFMC

| | MCAH | GCF | DFMC |
|---|---|---|---|
| **Sex (F:M)** | 3:1 [1] | 1:3 [9] | 1:1 [13] |
| **Age** | 50 (avg) [1] | <10 [9] | 20–50 [13] |
| **Size** | 0.2–1.5 cm [6] | 1–8 cm [8] | 0.3–4cm [13] |
| **Shape** | Papules, nodules [1] | Nodular [8] | Nodules, polyps, plaques |
| **Recurrence** | No [7] | Yes; 50% [11] | Yes; 14% [13] |
| **Metastasis** | No [2] | No [8] | Rare [13] |
| **Circumscription** | Well [2] | Poor [11] | Well to poor [13] |
| **Involvement** | Dermis [1] | Dermis, subcutis [11] | dermis, subcutis [13] |
| **Mitotic figures** | No [2] | Rare [8, 11] | 1–15/10 HPF [13] |
| **Atypical mitoses** | No [2] | No [8] | <20% of lesions [13] |
| **Necrotic focus** | No [2] | No [14] | <10% of lesions [13]<br>common in metastatic lesions [15] |
| **Epidermis** | Acanthotic [16] | Normal [11] | Acanthotic [17] |
| **Histiocytes** | Yes [2] | No [8] | Yes [18] |
| **Cellularity** | Hypercellular [2] | Hypocellular [11] | Hypercellular [18] |
| **Vascularity** | Proliferative [1] | Normal [11] | Normal [18] |
| **Sinusoidal spaces** | No | Yes [11] | No |
| **Inflammatory infiltrate** | Mixed: chronic lymphocytic, plasma cells, mast cells [1, 2] | Lymphocytic [11] | Lymphocytic and plasma cells [19] |
| **Inflammation** | Perivascular [1], extravascular [2] | Perivascular[11] | Extravascular, patchy [19] |

and notable perivascular inflammation [1]. Interestingly, it is associated with multi-angular or star-shaped multinucleate giant cells [2, 20, 21], which are also present in our case (Figure 1C). In contrast, GCF is a spindle-cell neoplasm of the dermis and subcutis that is lacking in haphazard proliferation of capillaries and venules seen in MCAH. Moreover, unlike MCAH, which is a hypercellular tumor, microscopic sections of GCF vary from cellular to hypocellular with myxoid appearance [11]. A prominent distinguishing feature of GCF is empty cleft-like "sinusoidal" or "pseudovascular" spaces lacking an endothelial or epithelial lining but are lined instead by spindle-shaped cells and multinucleated giant cells [11]. Additionally, GCF does not have mixed inflammatory infiltrate, but perivascular accumulation of lymphocytes in onionskin pattern [11]. Giant cell fibroblastoma lesions also have low-grade atypia and moderate pleomorphism, even though they are considered benign lesions [8]. It further distinguishes itself by its multinucleate giant cells that often have floret or wreath-like nuclear arrangement, and nuclear overlapping with modest and small or indistinct nucleoli (Table 2) [8].

Table 2: Multinucleated giant cell comparison in MCAH, GCF, and DFMC

| | Description | Nuclei | Nucleoli |
|---|---|---|---|
| **MCAH** | Multi-angular [2]<br>Star-shaped [2] | Palisading [13]<br>Hyperchromatic [2] | Prominent [16] |
| **DFMC** | Atypical, large, bizarre [13]<br>Touton [13]<br>Langhans [22, 23] | Bilobed, multilobed, oval [13]<br>Hyperchromatic [6]<br>Xanthomatous [13]<br>hemosiderin-positive [13] | Prominent [23] |
| **GCF** | Floret [8]<br>Wreath-like [8] | Hyperchromatic [8] | Indistinct [8] |

Although DFMC is a hypercellular dermal tumor like MCAH, it is distinguished histologically with its background of classical fibrous histiocytoma consisting of atypical bizarre "monster cells" with large, hyperchromatic, and hyperconvoluted nuclei with prominent nucleoli [17]. Dermatofibroma with monster cells has multinucleated cells that are highly pleomorphic with abundant foamy or hemosiderin-rich cytoplasm in most cases (Table 2) [13]. Unlike MCAH and GCF, DFMC lesions are also reported to have occasional Touton giant cells and Langhans giant cells [13]. Moreover, whereas MCAH has perivascular lymphocytic infiltrate, DFMC has a CD3+ lymphocytic and plasma cell infiltrate (Table 1) [19].

Immunohistochemically, MCAH, DFMC, and GCF have significant overlap, making distinguishing between the lesions difficult when relying on immunohistochemistry alone (Table 3). However, there are some notable differences reported in literature. For instance, MCAH and DFMC have positive immunoreactivity for CD68 [1, 19], whereas GCF is negative [14, 24, 25]. Based on our literature search, no study has verified immunoreactivity of Factor XIIIa for GCF, but has stipulated that it is likely negative based on several reports of childhood DFSP which have shown to be Factor XIIIa negative [26–28]. In comparison, MCAH and DFMC are positive for Factor XIIIa (Table 3) [1, 17]. Moreover, MCAH is CD34+ and S100–, whereas DFMC is CD34– and has focal S100 positivity (Table 3) [19]. Dermatofibroma with monster cells is hypothesized to be originating from dermal dendritic cells (dendrocytes) of monocyte-macrophage lineage which are also positive for Factor XIIIa and CD34. Although dendritic cells are usually positive for CD34, it is hypothesized that CD34-negativity in DFMC might be due to the fact that proliferating and differentiating dendritic cells lose their CD34 expression [19].

Table 3: Immunohistochemical comparison of MCAH, GCF, and DFMC

| | CD68 | Factor XIIIa | Vimentin | CD34 | S100 |
|---|---|---|---|---|---|
| **MCAH** | ± [1] | ± [1, 5] | + [1, 5] | + [1] | – [1] |
| **GCF** | – [14, 24] | – [25, 26] | + [29] | + [9, 29] | – [29] |
| **DFMC** | + [19] | + [17, 19] | + [19] | – [19] | + (focal) [19] |

Multinucleate cell angiohistiocytoma, GCF, and DFMC all are cutaneous lesions that contain multinucleated giant cells. These tumors considerably differ in rate of recurrences and have different prognostic implications. Therefore, they would require different levels of surveillance post-treatment. In our case, a change in diagnosis from DFMC and MCAH had significant implications. Since MCAH does not reoccur post-excision [7] as opposed to DFMC, the patient was discharged from clinician's care with no future follow-up scheduled. This highlights the importance in collating and analyzing the histopathological and immunohistochemical characteristics of the three lesions.

## CONCLUSION

Multinucleate cell angiohistiocytoma, DFMC, and GCF have several overlapping clinical and immunohistochemical characteristics. Although clinical presentation and immunohistochemistry aid in the diagnosis, it cannot be solely relied upon to differentiate MCAH from DFMC. Therefore, the diagnosis should be made after considering their histological characteristics supplemented by clinical presentation and immunohistochemical differences.

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## Author Contributions

Ahmed Shah – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Samih Salama – Conception of the work, Design of the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Gabriella Gohla – Conception of the work, Design of the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Salem Alowami – Conception of the work, Design of the work, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

## Guarantor of Submission

The corresponding author is the guarantor of submission.

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None.

## Consent Statement

This case does not use any specific patient identifiers, and the pictures are of microscopic histology and immunohistochemistry that cannot be used for patient identification purposes. In the department of pathology, we do not directly interact with patients, but all efforts have been made in great detail to anonymize the case as much as possible.

## Conflict of Interest

Authors declare no conflict of interest.

## Data Availability

All relevant data are within the paper and its Supporting Information files.