

## REVIEW PAPER

**MULTINUCLEATE CELL ANGIOHISTIOCYTOMA:  
A CASE SERIES AND LITERATURE REVIEW**

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Multinucleate cell angiohistiocytoma (MCAH) is a rare benign cutaneous entity. It classically presents as slowly progressive erythematous to violaceous papules on the distal extremities of middle-aged or elderly women. The entity may clinically resemble granuloma annulare, lichen planus, and several cutaneous vascular proliferations. Histologically, MCAH is characterized by vascular proliferation within the upper and mid-dermis, a mild perivascular inflammatory infiltrate, and characteristic bizarre-shaped multinucleate cells. To date, less than 200 cases have been reported in the literature. We present five of the best examples diagnosed in our department to further elucidate this peculiar entity for pathological recognition.

**Key words:** multinucleate cell angiohistiocytoma, multinucleate cells.

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**Introduction**

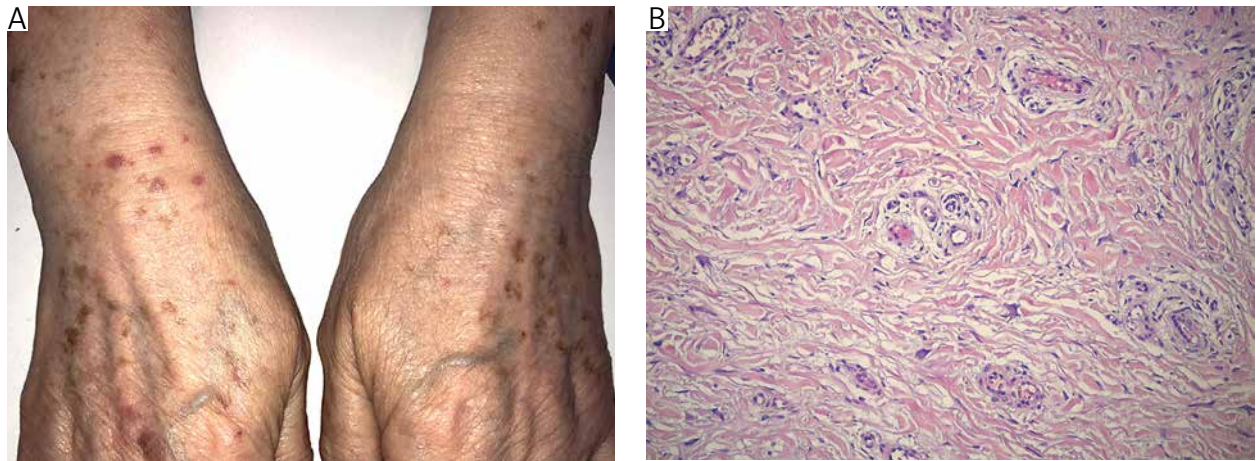
Multinucleate cell angiohistiocytoma (MCAH), first described in 1985 by Smith and Wilson-Jones [1], is a rare benign cutaneous entity. Although its exact etiology is unknown, it is considered to be a non-neoplastic vascular reactive process [2]. A hormonal pathogenesis has also been proposed given its overexpression of estrogen receptor alpha [3]. MCAH classically presents as slowly progressive, single or grouped erythematous to violaceous papules on the distal extremities of middle-aged or elderly women [4]. The condition often clinically resembles granuloma annulare, lichen planus, and cutaneous vascular proliferations such as angiofibroma, dermatofibroma, or Kaposi sarcoma [5].

Thus far, less than 200 cases of MCAH have been described in the literature. We report five cases of MCAH diagnosed in our department between the years 2015 and 2023 to further elucidate this peculiar entity based on our clinical experience and literature review.

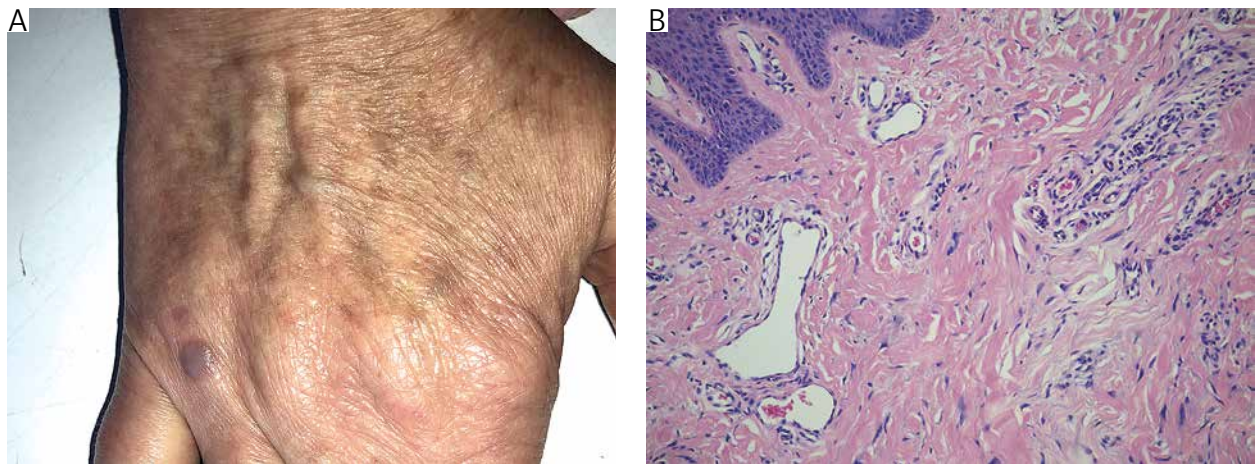
**Cases**

Case 1: A 75-year-old female patient presented with a 1-year history of multiple asymptomatic erythematous to violaceous papules on the dorsum of her right hand. During this period, no lesions spontaneously resolved. The patient also denied any previous local trauma in that area. Clinical examination revealed round, firm, non-desquamating papules with diameters ranging from 2 to 8 mm (Fig. 1A). A papule was excised for biopsy with a clinical suspicion of granuloma annulare. The biopsy revealed separated collagen fibers in the dermis, numerous capillaries with a sparse inflammatory infiltrate, and the presence of very characteristic dispersed stellate multinucleate cells (Fig. 1B). Histological findings supported a diagnosis of MCAH. One of the lesions resolved after cryotherapy.

Case 2: A 64-year-old female patient presented with two prominent violaceous papules on the dorsal aspect of her right hand. The lesions were asymptomatic and had developed over a period of one year. Clinical



**Fig. 1.** A) Well-demarcated multiple asymptomatic erythematous to violaceous papules on the dorsum of the right hand of a 75-year-old female patient. B) In the skin biopsy, there are numerous capillaries with a sparse inflammatory infiltrate and dispersed stellate multinucleate cells (H&E, 200×)



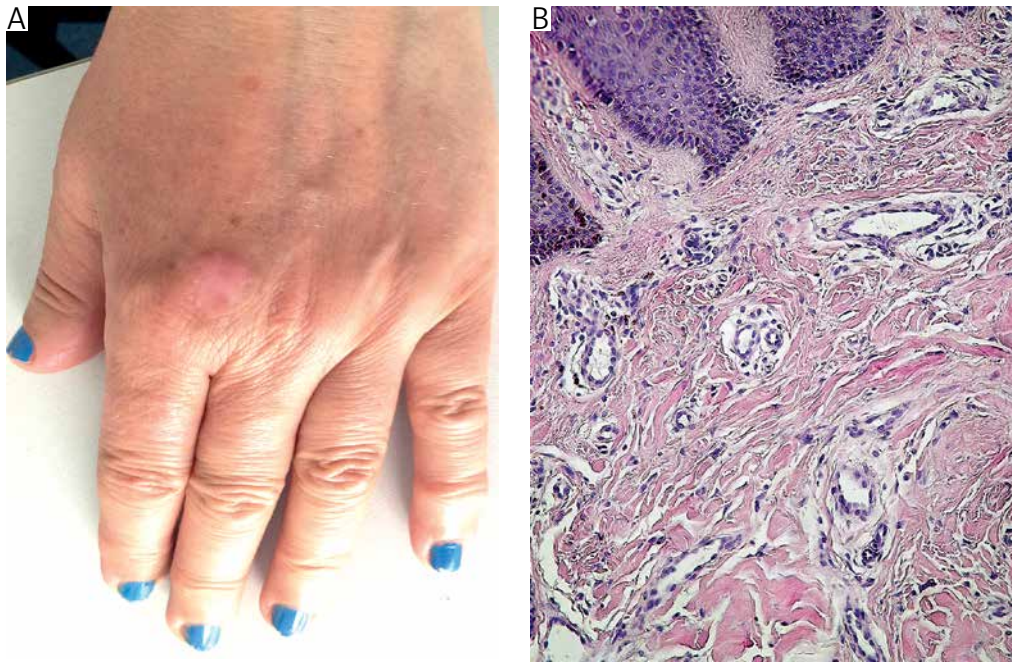
**Fig. 2.** A) Two prominent violaceous papules located on the dorsal part of the right hand of a 64-year-old female patient. B) In the skin biopsy, there are dilated blood vessels of variable caliber with an accompanying lymphohistiocytic inflammatory infiltrate and angular spindle bizarre-shaped multinucleate cells in the fibrous stroma (H&E, 200×)

examination revealed smooth, round papules with diameters ranging from 2 to 7 mm (Fig. 2A). Cutaneous lymphoma or pseudolymphoma was suspected clinically. Histological findings revealed dilated blood vessels of variable caliber with an accompanying lymphohistiocytic inflammatory infiltrate and bizarre-shaped multinucleate cells in the fibrous stroma (Fig. 2B). The diagnosis of MCAH was made. Treatment options such as cryotherapy or intralesional corticosteroids were entertained, but the patient ultimately declined treatment due to the benign nature of the lesions.

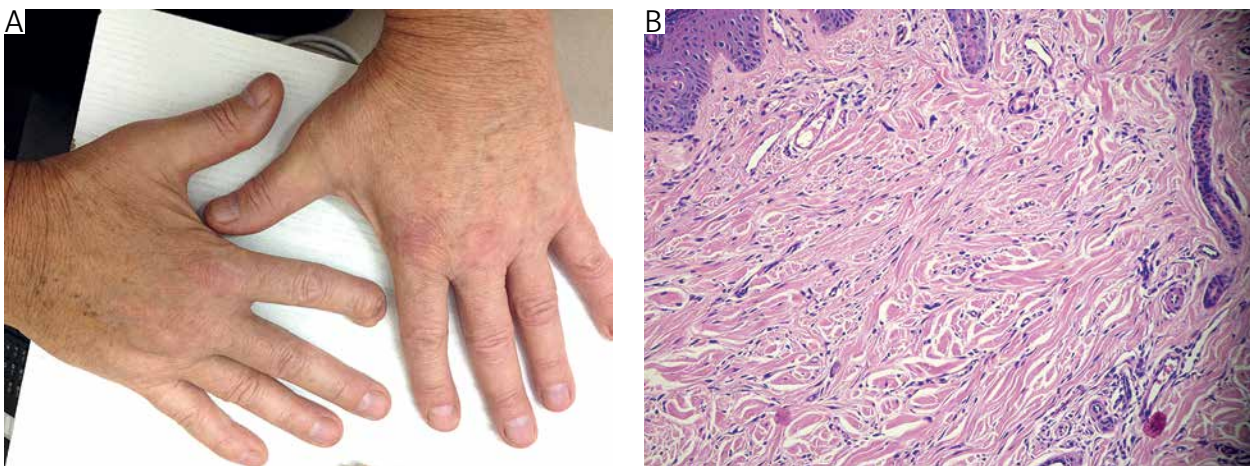
**Case 3:** A 53-year-old female patient presented with one asymptomatic erythematous plaque-like lesion on the dorsum of her left hand. The lesion had been present for two years. Clinical examination revealed firm, round, coalescing papules forming a semi-annular plaque-like lesion (Fig. 3A). Granuloma annulare was suspected clinically. A biopsy of the lesion showed a hyperplastic epidermis with basal

hyperpigmentation, and proliferation of dilated blood vessels in the fibrotic dermis with sparse angulated spindle cells in the interstitium corresponding to MCAH (Fig. 3B). The patient considered cryotherapy but, in the end, declined any treatment.

**Case 4:** A 60-year-old male patient presented with multiple erythematous papules and plaques on his bilateral dorsal hands. Clinical examination revealed grouped papules with diameters ranging from 2 to 3 mm (Fig. 4A). The lesions had developed over the course of two years. One papule was excised for biopsy with a clinical suspicion of granuloma annulare. Microscopic examination presented a fibrotic dermis with the proliferation of mid-sized post-capillary venules, numerous spindle and angular-shaped mononuclear cells with single multinucleate cells dispersed between collagen bundles (Fig. 4B). The diagnosis of MCAH was established. The patient declined any form of treatment.



**Fig. 3.** A) Firm, round, coalescing papules forming a semi-annular plaque-like lesion on the left dorsal hand of a 53-year-old female patient. B) In the skin biopsy, there is proliferation of dilated blood vessels in the fibrotic stroma with sparse angulated spindle cells in the interstitium (H&E, 200 $\times$ )

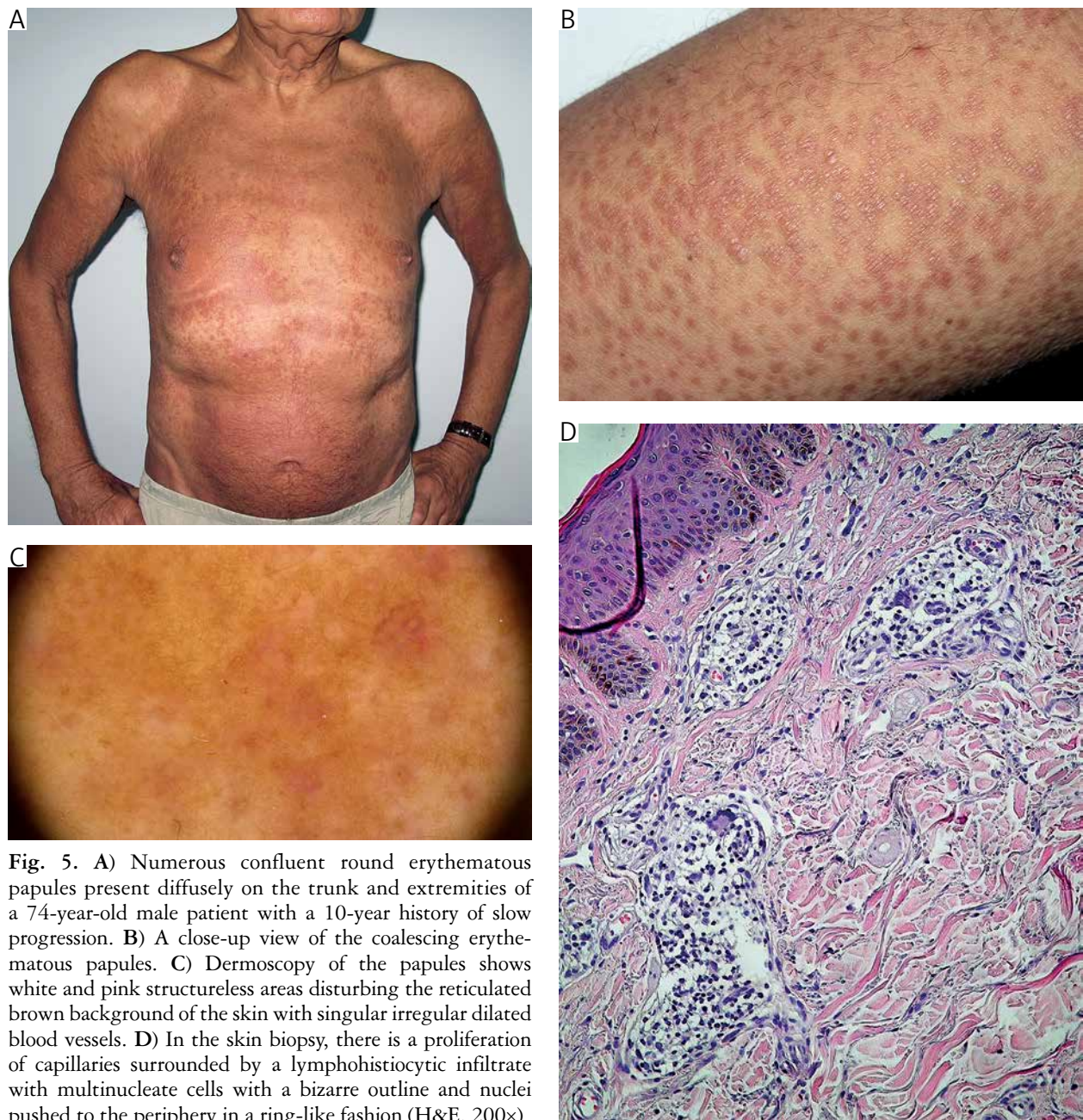


**Fig. 4.** A) Multiple erythematous papules and plaques located bilaterally on the dorsal hands of a 60-year-old male patient. B) In the skin biopsy, there is proliferation of post-capillary venules, numerous spindle and angular-shaped mononuclear cells, and single multinucleate cells dispersed between collagen bundles (H&E, 200 $\times$ )

Case 5: A 74-year-old male patient presented with a 10-year history of slowly progressive erythematous papules present diffusely on his trunk and extremities (Fig. 5A). Clinical examination revealed numerous confluent round papules with diameters ranging from 2 to 4 mm (Fig. 5B). Diffuse granuloma annulare or granulomatous dermatitis was suspected clinically. Dermoscopy revealed asymmetric white and pink structureless areas disturbing the reticulated brown background of the skin with singular irregular dilated blood vessels (Fig. 5C). Histological examination of the two lesions showed similar findings, such as

the proliferation of capillaries surrounded by a moderate lymphohistiocytic inflammatory infiltrate with bizarre-shaped multinucleate cells (Fig. 5D). The mentioned phenomena favored a diagnosis of MCAH, in this case a generalized form of MCAH. The patient was treated with topical corticosteroids and PUVA therapy with little improvement. He later developed mycosis fungoides and was treated with systemic methotrexate at another center.

All clinical features of the described MCAH cases are summarized in Table I.

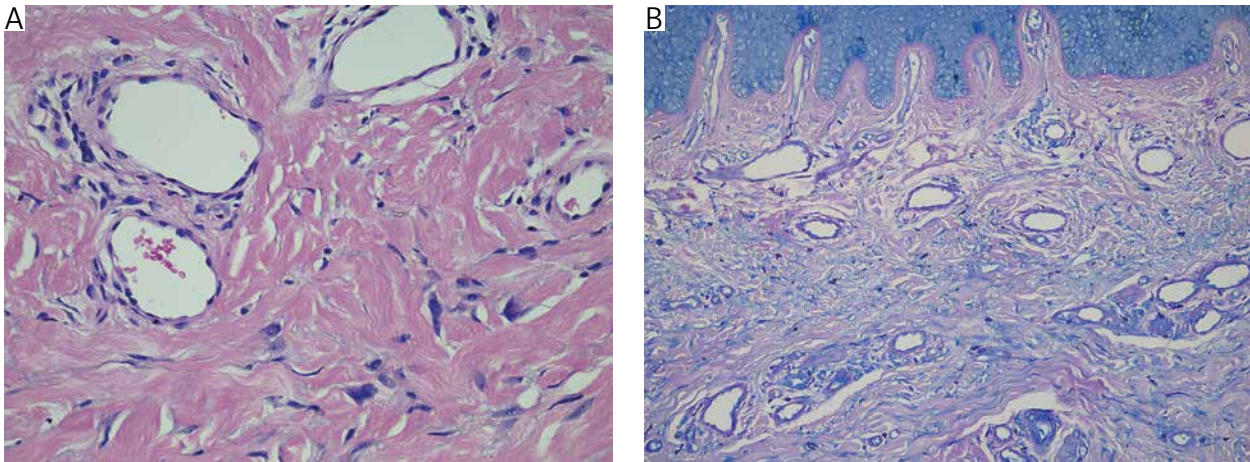


**Fig. 5.** A) Numerous confluent round erythematous papules present diffusely on the trunk and extremities of a 74-year-old male patient with a 10-year history of slow progression. B) A close-up view of the coalescing erythematous papules. C) Dermoscopy of the papules shows white and pink structureless areas disturbing the reticulated brown background of the skin with singular irregular dilated blood vessels. D) In the skin biopsy, there is a proliferation of capillaries surrounded by a lymphohistiocytic infiltrate with multinucleate cells with a bizarre outline and nuclei pushed to the periphery in a ring-like fashion (H&E, 200×)

**Table I.** Clinical features of multinucleate cell angiohistiocytoma cases

CASE NUMBER	SEX	AGE (YEARS)	NUMBER OF LESIONS	DURATION (YEARS)	LOCATION	COLOR	CLINICAL DIAGNOSIS
1	F	75	Multiple	1	Dorsum of right hand	Red-purple	Granuloma annulare
2	F	64	Multiple	1	Dorsum of right hand	Purple	Cutaneous lymphoma or pseudolymphoma
3	F	53	Multiple	2	Dorsum of left hand	Red	Granuloma annulare
4	M	60	Multiple	2	Bilateral dorsal hands	Red	Granuloma annulare
5	M	74	Multiple	10	Diffuse	Red	Granuloma annulare or granulomatous dermatitis

F – female, M – male



**Fig. 6.** A) The hallmark histological features of multinucleate cell angiohistiocytoma (MCAH) are the proliferation and dilation of blood vessels with prominent endothelial cells in the upper and mid-dermis, and the presence of bizarre-shaped multinucleate cells with angulated basophilic cytoplasm (H&E, 400 $\times$ ). B) The presence of mast cells between collagen bundles detected with Giemsa staining may be a helpful sign in MCAH (H&E, 200 $\times$ )

Routine laboratory tests such as complete blood count, blood glucose level, liver function tests, kidney function tests, thyroid function tests, and urinalysis were all within the normal range.

In order to sum up the most specific histological findings in all five patients diagnosed with MCAH, it is important to consider the following points:

- the overlying epidermis may be hyperplastic due to acral location, with proper maturation and cornification of keratinocytes in the majority of cases, indicating that MCAH is a dermal process;
- the basal cell layer may be hyperpigmented, as it was in three of our five cases;
- vascular proliferation and dilation with prominent endothelial cells, confined to the upper and mid-dermis, is a hallmark;
- the perivascular inflammatory infiltrate is usually sparse;
- the presence of bizarre-shaped cells of fibrohistiocytic nature with angulated basophilic cytoplasm and several peripherally located hyperchromatic nuclei is characteristic (Fig. 6A);
- the stroma may be fibrotic;
- a helpful sign may be the presence of mast cells detected between collagen bundles, as was already described [6], and is revealed with Giemsa staining (Fig. 6B).

## Discussion

MCAH is infrequently diagnosed. To date, approximately 200 cases, including our five, have been reported in the literature. It is believed to be underdiagnosed due to the lack of awareness of this entity among physicians [2]. Based on an analysis of 142 documented cases, the average age at onset was found to be 50.1 years, with the vast majority (79%) being female [7]. In the present group of patients,

the average age of onset was 65.2 years. We present here the best examples of MCAH based on clinical presentation, histology, and follow-up. However, in the years 2015–2023, 15 cases of MCAH were diagnosed in our department. The most common locations of lesions included the dorsal hand (13 cases, 86.7%), thigh (1 case, 6.6%), and 1 generalized form of MCAH (6.6%). The majority of cases occurred in women (11 cases, 73.3%).

To this day, the pathogenesis of MCAH remains controversial. The condition is believed to be a reactive process involving vascular proliferation. One theory suggests that interactions between fibrohistiocytic cells and mast cells may lead to the release of angiogenic cytokines [6]. MCAH lesions have also demonstrated overexpression of estrogen receptor alpha [3]. This finding may explain its marked female predominance. Despite its clinical resemblance to Kaposi sarcoma, MCAH has not been found to be associated with human herpesvirus-8 (HHV-8) [5].

MCAH typically follows an indolent course. Although there have been cases of single lesions, multiple lesions, often occurring bilaterally, are more frequently observed [4]. All of our patients presented with multiple lesions. Most lesions were unilateral; however, two patients presented with bilateral lesions. One of our patients even presented with the rare generalized form of the condition, first described in 1996 [8]. Lesions typically have a smooth or occasionally scaly surface and a diameter of less than 1 cm. The classic distribution of the lesions is over the distal extremities, the most common being the dorsal hands, followed by the thighs and legs [4]. Less commonly, the face and trunk may be affected. Although very rare, mucosal involvement has also been reported [9]. In most cases, the lesions are asymptomatic; however, they can be pruritic [10]. Spontaneous remission of the entity is possible but infrequent [4, 7].

**Table II.** Differential diagnosis of multinucleate cell angiohistiocytoma

DISEASE	HISTOLOGICAL FEATURES
Granuloma annulare	A dermal process consisting of a central core of degenerative collagen with mucinous changes, surrounded by radially distributed histiocytes.
Lichen planus	A lichenoid dermatosis with basal cell vacuolization, degeneration, subepidermal cleft formation, and a dense band-like lymphocytic infiltrate at the dermal-epidermal junction with scattered colloid bodies and melanophages.
Angiofibroma	A dermal irregular proliferation of blood vessels with collagen bundle formation.
Dermatofibroma	A dermal tumor composed of fascicles of spindle cells arranged in a storiform pattern with histiocytes, multinucleate giant cells, hemosiderin deposits, and thin-walled blood vessels.
Kaposi sarcoma	A dermal proliferation of endothelial spindle cells forming irregular vascular channels and slits with hemorrhage, hemosiderin deposits, and an admixture of plasma cells.

The clinical differential diagnosis of MCAH includes granuloma annulare, lichen planus, angiofibroma, dermatofibroma, and Kaposi sarcoma [5, 6]. The characteristic histological features of the mentioned diseases are presented in Table II.

Granuloma annulare is characterized by the presence of focal collagen degeneration with mucin deposition, surrounded by radially distributed histiocytes with an accompanying perivascular lymphocytic inflammatory infiltrate [11]. In lichen planus, a lichenoid dermatosis, features such as basal cell vacuolization with a dense band-like lymphocytic infiltrate at the dermal-epidermal junction with scattered colloid bodies and melanophages are typically observed. Often clefts between the degenerated basal layer and dermis, referred to as Max Joseph spaces, are formed. Typically, the epidermis demonstrates hyperkeratosis, irregular acanthosis, and hypergranulosis [12]. Angiofibroma presents with an increased number of dilated blood vessels, but with fewer multinucleate cells, and the collagen bundles are vertically oriented. Dermatofibroma is a tumor composed of spindle cells within a loose collagenous stroma mixed with histiocytes, multinucleate giant cells, hemosiderin deposits, and thin-walled blood vessels. A typical feature is the presence of collagen trapping at the periphery of the lesion, while the overlying epidermis usually exhibits epidermal hyperplasia with occasional basaloid induction [13]. Kaposi sarcoma corresponds to the proliferation of HHV-8 positive endothelial cells in the dermis, surrounded by an admixture of plasma cells. These endothelial spindle cells form irregular vascular channels and slits, with hemorrhage and hemosiderin deposition [5].

A skin biopsy is required for an appropriate diagnosis of MCAH. Additionally, awareness of this rare entity is necessary in order to include it in the differential diagnosis. Histologically, MCAH is characterized by the presence of vascular hyperplasia, composed primarily of thin-walled post-capillary venules and capillaries, limited to the upper and mid-dermis.

The lumina of the vessels may be dilated or narrow, and they are typically lined with a layer of endothelial cells. Occasionally, the vessels may also be lined with lymphocytes. Fibrohistiocytic mononuclear cells are usually present. Collagen bundles tend to be thickened and hyalinized. The epidermis may be normal or hyperplastic. Bizarre-shaped multinucleate cells are not pathognomonic for MCAH but are the most characteristic feature [4, 6].

Treatment of MCAH is not necessary in most cases due to its benign nature. The lesions also tend to develop slowly, as demonstrated by our cases. However, in some cases, particularly in cases of symptomatic or generalized lesions or for cosmetic purposes, lesions may be treated using surgical excision, topical or intralesional corticosteroids, cryotherapy, or laser therapy [10]. The variable success of these treatment modalities has been reported. Often, multiple methods must be combined in order to obtain satisfactory results. Following an inadequate response to monotherapy with intralesional corticosteroids, successful treatment of MCAH with the combined use of intralesional corticosteroids and a potassium-titanyl-phosphate laser in a 67-year-old male patient was reported [14]. Our own clinical experience has demonstrated several limitations of the available therapeutic options.

## Conclusions

MCAH is a peculiar entity that is still largely unfamiliar to medical professionals. To the best of our knowledge, these are the first cases reported from Poland. Although rare, MCAH should be considered in the context of characteristic clinical and histological findings. It typically occurs on the dorsal hands of middle-aged or elderly women. It should be kept in mind in the context of multiple progressive erythematous lesions resembling granuloma annulare. Also, it should be emphasized that the presence of multinucleate cells, which may appear in other inflam-

matory, neoplastic, and reactive processes, is neither exclusive nor pathognomonic for MCAH. However, their dispersed presence in the context of dermal vascular proliferation with accompanying mast cells may be considered a key finding in this infrequent entity.

## Disclosures

1. Institutional review board statement: Not applicable.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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