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Clinical and dermoscopic assessment of angiosarcoma: a diagnostic classification for early detection

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Abstract

Cutaneous and mucosal angiosarcoma (CMA) is a rare and aggressive tumor of vascular endothelial cells that can occur in any body site, including the skin and mucosa. A history of radiation and chronic lymphedema are well-established risk factors, but the causes of sporadic CMA are less clear. Dermoscopy has emerged as a useful noninvasive tool that can aid in diagnosing cutaneous tumors, including CMA, by providing magnified images of the skin surface and subsurface structures. However, to date, little is known about the dermoscopic patterns of CMA. This study aimed to evaluate the clinical and dermatoscopic features of CMA in order to create a classification that can be useful in the early diagnosis of this rare but fearful tumor. A descriptive, retrospective analysis was conducted on the clinical and dermoscopic characteristics of histopathologically confirmed cases of CMA. The study population consisted of 10 patients with a histologically confirmed diagnosis of CMA, including 6 males (60%) and 4 females (40%). By analyzing our cases clinically and dermoscopically, we classify them into three configurations to facilitate an early and more accurate diagnosis: melanoma-like pattern, benign vascular-like pattern (both cutaneous and mucosal), and inflammatory-like pattern. The identification of CMA poses a diagnostic dilemma for clinicians, as its clinical presentation often overlaps with other benign and malignant dermatological conditions. Dermoscopy, although it does not provide specific or pathognomonic parameters, may improve the diagnostic accuracy of these lesions in conjunction with clinical and histological features. For the first time in the literature, we have attempted to classify the extreme clinical and dermoscopic polymorphism of angiosarcoma by describing three patterns that can be extremely useful for achieving an early and accurate diagnosis of this fearsome and aggressive tumor.

Key words: skin cancer; dermoscopy; vascular lesion.

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Introduction

Angiosarcoma is a rare and aggressive tumor of vascular endothelial cells that can occur in any body site, including the skin and mucosa. It is characterized by a high rate of disease recurrence and mortality.[1] The US incidence of angiosarcoma doubled between 2001 and 2019, and in 2020, the reported incidence rate was 3.0 cases per 1,000,000 person-years.[1]

Cutaneous and mucosal angiosarcoma (CMA) typically occurs in the elderly, with an average age at presentation of 73. A history of radiation and chronic lymphedema are well-established risk factors, but the causes of sporadic CMA are less clear. UV radiation, immunocompromised states, arteriovenous fistulas, and xeroderma pigmentosum have also been proposed as potential risk factors.

CMA is marked by an infiltrative and aggressive nature. It is subdivided into classic angiosarcoma of the scalp, face, and neck of the elderly; angiosarcoma secondary to chronic lymphedema (Stewart-Treves syndrome); and angiosarcoma arising in irradiated skin areas.

CMA commonly occurs in the head and neck region, particularly on the scalp.[2] However, it can also arise in other body sites, such as the breast region, shoulders, and tongue.

CMA is considered the skin tumor with the poorest prognosis, with metastasis occurring in 36.3% of cases.[3] Aggregate five-year survival was 31.6% with a median survival of 25 months. The best five-year survival was in the radiation-associated subtype (48.8%), whereas the worst was in the Stewart-Treves subtype (21.6%).[3]

Despite CMA's aggressive biology, its clinical presentation is often innocuous. It may present as a slow-growing, asymptomatic lesion that can easily be misdiagnosed as a benign vascular tumor or other non-neoplastic condition. Thus, delayed diagnosis and treatment can lead to poor outcomes, with a high rate of local recurrence, distant metastasis, and mortality; as such, arriving at a prompt diagnosis can be highly challenging.

A differential diagnosis of CMA includes multiple entities. It has been reported to resemble various dermatoses, such as inflammatory, autoimmune, and infectious diseases, benign and malignant tumors, and post-traumatic lesions.[4] Indeed, it can present

with a variety of clinical features, such as a localized, well-defined tumor or diffuse, multifocal lesion with indistinct margins, ranging from subtle erythematous patches to purplish-red nodular, infiltrative, or ulcerative lesions. Tissue infiltration, edema, ulceration, and hemorrhage can develop with increasing tumor size. CMA may resemble a hematoma-like lesion, rosacea, eczema, hemangioma, cellulitis, or facial and eyelid angioedema. Not uncommonly, advanced lesions can mimic epithelial neoplasms, including squamous cell carcinoma, keratoacanthoma, basal cell carcinoma, atypical fibroxanthoma, and amelanotic malignant melanoma.[5]

Diagnosing CMA is often challenging, and a biopsy of the lesion is necessary for an accurate diagnosis. Histologically, CMA often reveals an irregular vascular proliferation composed of endothelial cells with high mitotic activity, pleomorphism, and nuclear atypia with a markedly hemorrhagic background. The tumor cells may be arranged in sheets, nests, or cords, and they may infiltrate the surrounding dermis and subcutaneous tissue.

Immunohistochemistry analysis is also helpful in confirming the endothelial origin of the tumor, with markers such as CD31, CD34, and factor VIII-related antigens being positive in most cases.[6,7] Dermoscopy has emerged as a useful noninvasive tool for diagnosing cutaneous tumors, including CMA,[8] by providing magnified images of the skin surface and subsurface structures. However, little is known about the dermoscopic patterns of CMA to date. Dermoscopic features of CMA have been reported, but most of the existing literature is limited to a few case series and case reports. Most of these studies have focused on a single anatomical site or included only small sample sizes. Based on the currently available published data, CMAs appear to be characterized predominantly by nonspecific dermoscopic features. In this study, we retrospectively analyze cases of cutaneous angiosarcoma from a clinical and dermoscopic point of view in order to propose a classification that can be useful in the early diagnosis of this rare but fearful tumor.

Materials and Methods

We conducted a retrospective descriptive analysis of the clinical and dermoscopic characteristics of histopathologically proven CMA. Data on sociodemographic variables, clinical, and dermoscopic characteristics were collected from the databases of two Italian Dermatology Units (Firenze and Meldola-Forlì). All the patients included in the study were independently diagnosed. According to the protocols in force in each center, each lesion was photographed clinically and dermoscopically before surgical excision of the primary CMA. Patients and legal guardians (when needed) were informed about the study, and written informed consent for publication of the photographs used in this manuscript was obtained. CMAs histopathologically diagnosed between 2016 and 2023 were eligible for the current analysis. All lesions were examined by dermatopathologists specializing in the diagnosis of skin tumors. The equipment used for dermoscopic examinations consisted of a handheld dermatoscope (Heine Delta 20, Heine Optotechnik, Herrsching, Germany). Both clinical and dermoscopic images of all lesions were captured with a high-resolution compact digital photographic camera (Olympus Digital model no. E-520, a 7.1-megapixel digital photo camera with a 3.8 optical zoom lens, a focal length of 28 to 105 mm in a 35 mm format, and a maximum lens aperture of f/2.8-f/5.8). Dermoscopic images were captured with Dermaphot (Heine Optotechnik, Herrsching, Germany), which connects the dermatoscope to the camera to generate reproducible, high-quality dermoscopic pictures at 10x magnification in JPEG file format. These clinical and dermoscopic images and the data were stored on a common Windows-based personal computer.

We performed a clinical evaluation of the morphological characteristics of each assessed CMA. Three investigators (BZ, IS, and VDG), with expertise in pigmented lesions and dermoscopy, analyzed the archived digital dermoscopic images and completed a printed questionnaire to categorize the lesions according to atypical dermoscopic pattern analysis. The dermoscopic pattern and the presence or absence of dermoscopic features in a given lesion were defined by the agreement of at least two of the three dermoscopists.

Results

The study population consisted of 10 patients with a histologically confirmed diagnosis of CMA, including 6 males (60%) and 4 females (40%). Their age at presentation ranged from 54 to 84 years (mean 67.6 years, median 71 years). The anatomical sites were as follows: breast (40%), head and neck (30%), upper extremities (20%), and mucosa (tongue, 10%). All female cases had a history of previous breast cancer, and the CMAs were localized in the breast region. Clinically, 60% of the lesions were pigmented and palpable. The remaining 40% of the lesions were achromic and always related to previous breast cancer and radiotherapy. Thirty percent of the lesions were ulcerated or abraded on the surface. Dermoscopically, none of the lesions showed typical melanocytic features, such as pigment network, globules, streaks, or pseudopods. Most cases (60%) were characterized by the presence of blue-violet areas with various intensities and shades depending on the different anatomical locations.

Clinical-dermoscopic patterns

By analyzing our cases clinically and dermoscopically, we classify them into three configurations to facilitate an early and more accurate diagnosis: melanoma-like pattern, benign vascular-like pattern (both cutaneous and mucosal), and inflammatory-like pattern.

Melanoma-like pattern

Normally localized at the scalp level, melanoma-like patterns present clinically in the form of a partially pigmented nodular lesion with irregular and ill-defined edges, with areas of abrasion, infiltrating the underlying tissues with rapid growth (Figure 1A). In the more advanced stages, satellite lesions are frequently detected. Dermoscopically, this pattern is characterized by the presence of red-blue-purple areas confluent with each other (Figure 1B), which can simulate the bluish-white veil typical of melanoma. The clinical and dermatoscopic presentation may be suggestive of a melanoma. Still, the lack of typical dermoscopic parameters for a melanocytic lesion allows us to exclude it with a good probability. The pathognomonic dermoscopic parameter for angiosarcoma is a sort of carpet made up of red-brown islands that surrounds the primary lesion (Figure 1C). Satellite lesions had dark red and purple hemorrhagic clots (Figure 1D).

Benign cutaneous vascular-like pattern

Clinically, this pattern is characterized by a pigmented nodular lesion with bluish shades and a smooth surface with well-defined margins; it is non-ulcerated but infiltrated (Figure 2A). The lesion normally feels hard to the touch and grows rapidly. This pattern is

characterized dermoscopically by the presence of bluish lacunae well delimited by whitish fibrous septa (Figure 2B). This dermoscopic picture is similar to angiokeratomas but is distinguishable due to the characteristics of the septa of angiosarcomas, which appear thicker, wider, and coarser, causing a clear demarcation between the lacunae. Furthermore, the presence of red dots frequently found on the septa and surrounding the bluish lacunae represents a typical dermoscopic parameter for angiosarcoma (Figure 2B).

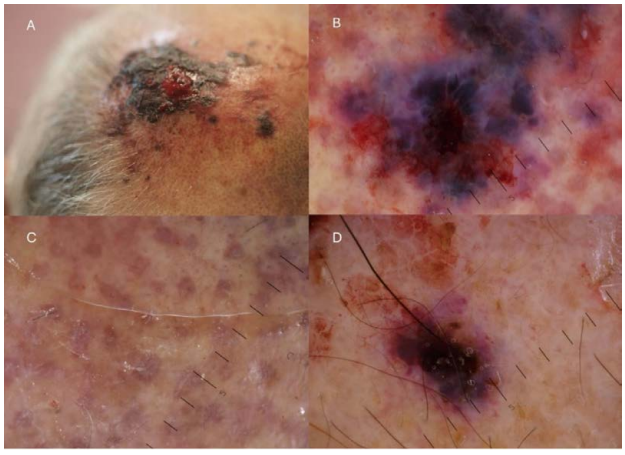

Figure 1. An 81-year-old man with angiosarcoma of the scalp (melanoma-like pattern). **A**) Clinically, a partially pigmented nodular lesion with irregular and ill-defined edges, with abrasion areas, infiltrating the underlying tissues with rapid growth. **B**) Dermoscopically, this pattern is characterized by the presence of red-blue-purple areas, confluent with each other, which can simulate the bluish-white veil typical of melanoma. **C**) Dermoscopically, a typical parameter for angiosarcoma is detected: a carpet formed by red-brown islands surrounding the primary lesion. **D**) Dermoscopically, satellite lesions had dark red and purple hemorrhagic clots.

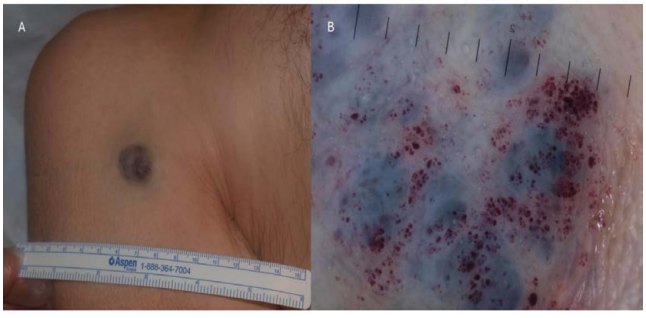

Figure 2. A 56-year-old man with angiosarcoma of the right shoulder (benign cutaneous vascular-like pattern). **A**) Clinically, pigmented nodular lesion with bluish shades, smooth surface, and well-defined margins. **B**) Dermoscopically, bluish lacunae well delimited by whitish fibrous septa. This dermoscopic picture is similar to angiokeratomas but is distinguishable due to the characteristics of the septa of angiosarcomas, which appear thicker, wider, and coarser, causing a clear demarcation between the lacunae. Furthermore, red dots frequently found on the septa and surrounding the bluish lacunae represent a typical dermoscopic parameter for angiosarcoma.

Benign mucosal vascular-like pattern

At the mucosal level, an even rarer site, angiosarcoma clinically presents with a palpable bluish lesion detected on the mucosal surface; it is not abraded and is asymptomatic (Figure 3A). On dermatoscopic examination, these lesions appear as a bluish homogeneous area that tends to whiten towards the periphery with light punctiform vessels that fade centrally towards the periphery (Figure 3B). A differential diagnosis mainly includes hemangioma, which appears soft upon palpation, while mucosal angiosarcomas are extremely hard.

Inflammatory-like pattern

This was the most frequent clinical-dermoscopic pattern (40%) and, in our series, it was always correlated to a previous breast carcinoma and radiotherapy. Clinically, it presents as ring-shaped cutaneous patches with a slightly lighter and atrophic center and a slightly infiltrated, red-purplish border (Figure 4A). Some areas present purpuric elements; some patches tend to be confluent. Unlike other patterns, the lesions show extremely slow growth, without significant symptoms. Dermoscopy revealed pink-purple "steam-like areas"[9] with a white or skin-colored central area and a more intense purple coloration at the periphery of the lesions (Figure 4B).

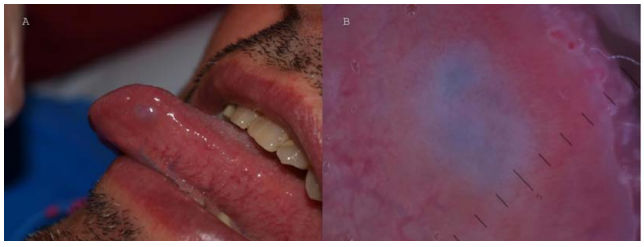

Figure 3. A 54-year-old man with angiosarcoma of the tongue (benign mucosal vascular-like pattern). **A**) Clinically, palpable bluish lesion detected on the mucosal surface; it is not abraded and is asymptomatic. **B**) Dermoscopically, bluish homogeneous area that tends to whiten towards the periphery with light punctiform vessels.

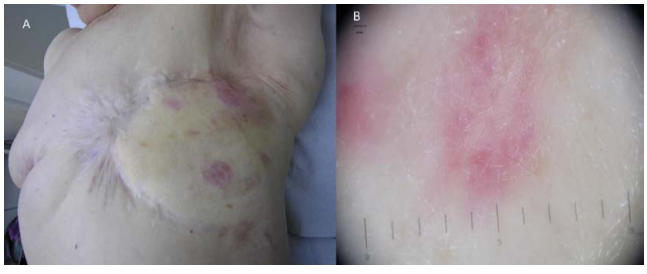

Figure 4. A 72-year-old woman with angiosarcoma of the breast region and a history of breast carcinoma treated with radiotherapy (inflammatory-like pattern). **A**) Clinically, ring-shaped cutaneous patches with a slightly lighter and atrophic center and a slightly infiltrated red-purplish border. **B**) Dermoscopy revealed pink-purple "steam-like areas" with a white or skin-colored central area and a strengthening of the purple color at the periphery of the lesions.

A differential diagnosis includes inflammatory lesions, like granuloma annulare. Immunohistochemistry can reveal tumor cells $CD31^+$, $CD34^+$, and $D2\text{-}40^+$, supporting a final diagnosis of well-differentiated CMA.

Discussion

The identification of CMA poses a diagnostic dilemma for clinicians, as its clinical presentation often overlaps with other benign and malignant dermatological conditions.

In the present study, the preoperative diagnosis was correct in only one case (10%), a 72-year-old woman with a history of breast carcinoma treated with radiotherapy. In fact, CMA presents an extreme clinical and dermoscopic polymorphism with a variety of highly nonspecific dermoscopic patterns, making it difficult, if not impossible, to make a dermoscopy-based diagnosis of the tumor.

In this study, we tried to identify some recurrent clinical and dermoscopic patterns to improve diagnostic accuracy. Our observation of a melanoma-like pattern in 30% of cases of CMA underscores the importance of dermatoscopic evaluation in distinguishing between these entities. This pattern presented red-blue-purple areas of different dimensions with irregular arborizing vessels surrounding and crossing the surface of the lesions.[10] CMA may demonstrate irregular or haphazardly arranged vessels with areas of hemorrhage or necrosis in the context of a rapidly growing lesion with aggressive behavior, necessitating high suspicion for an accurate diagnosis. This red-blue-purple pattern enters into the differential diagnosis with melanoma, particularly when a whitish-blue veil is present. However, the absence of dermoscopic features indicative of melanocytic proliferation in CMA allows for a confident diagnosis. In scalp lesions, we identified a dermoscopic parameter typical of angiosarcoma, characterized by the presence of non-palpable red-brown islands at the periphery of the lesion, surrounding the main tumor mass (Figure 1C).

The identification of a benign vascular-like pattern in certain cases of CMA highlights the diagnostic challenges posed by its resemblance to benign vascular proliferations, both at the skin and mucous membrane levels.

Mucosal angiosarcomas are extremely rare, comprising only 2% of all angiosarcomas.[11] Mucosal and salivary gland angiosarcomas are mostly presented as single case reports.[12-15] Documentary evidence points to the rare presence of the lesion in the oral cavity. In our group of 10 patients, we had only one case of mucosal angiosarcoma, localized at the tongue level.

Dermatoscopy of oral angiosarcoma may demonstrate a bluish homogeneous area that tends to whiten towards the periphery, presenting the classic colors of vascular lesions. In mucosal cases, CMAs exhibit non-specific dermoscopic features; however, these lesions are notably firm upon palpation, in contrast to benign vascular lesions, which are exceedingly soft and nearly vanish under acupressure. In fact, a harder consistency and the fact that it grows rapidly can help differentiate CMA from benign entities, especially in cases where clinical suspicion is high.

The case posed a diagnostic challenge due to the extreme rarity of angiosarcoma of the tongue, a malignancy of the head and neck region, which is infrequently considered in the differential diagnosis of tongue lesions and rarely identified clinically. At the cutaneous level, with the exception of the scalp and the breast region, in our series, the benign vascular-like pattern is characterized by the presence of a pigmented nodular lesion with bluish shades and a smooth surface with well-defined margins that infiltrate the underlying tissues. Dermoscopically, these lesions exhibit bluish lacunae distinctly bordered by whitish fibrous septa, necessitating a differential diagnosis with benign vascular lesions like angiokeratomas. A correct diagnosis is possible thanks to red dots appearing dermoscopically above the fibrous septa surrounding the lacunae, which are never found in angiokeratomas or other benign vascular lesions (Figure 2B).

The inflammatory-like pattern was the most frequent in our series (40%) and is closely related to a history of breast cancer and subsequent radiotherapy. Furthermore, our characterization of an inflammatory-like pattern in some cases of CMA emphasizes the diverse clinical manifestations of this malignancy and the potential for diagnostic ambiguity.[16] This pattern typically appears homogenous and structureless with a whitish-pink area, a characteristic well-documented in the literature. Lesions exhibit less intense and variable colors compared to tumors on the scalp or face. Dermatoscopically, CMA shows whitish veil areas with a central region that is either white or skin-colored, along with an intensification of the purple color at the edge of the lesion. A differential diagnosis included inflammatory lesions, like granuloma annulare, purpuric dermatoses, or urticarioid skin manifestations. The critical aspect is that these lesions are unresponsive to corticosteroid therapy and asymptomatic.

Various dermatoscopic aspects suggestive of CMA have been documented in the literature. Sporadic angiosarcoma typically presents as patchy, structureless, variable red (light and dark) to purple or purple to bluish areas interspersed with small yellow globular structures.[17] Oiso *et al.*[18] observed a color gradation within lesions on dermatoscopy that correlated with a high percentage of tumor cells on histology. Another study by De Giorgi *et al.*[19] identified pink-violet "steam-like areas" as a significant dermatoscopic feature for characterizing angiosarcoma. Additionally, Oiso *et al.*[18] demonstrated that vascular structures, such as vessels or lacunae, were not observed as dermatoscopic features of angiosarcoma, potentially supporting its differentiation from other vascular tumors like hemangioma or angiokeratoma.

Dermoscopy, even if it does not present specific or pathognomonic parameters, may enhance the diagnostic accuracy of these lesions along with clinical and histological features. In any case, CMA clinical and dermoscopic presentation is remarkable for its polymorphism and consequent differential diagnostic challenge with melanocytic and non-melanocytic skin tumors, both benign and malignant, and with inflammatory disease. Thus, histopathological examination is mandatory and represents the diagnostic gold standard. An incisional biopsy may not represent the tumor in its entirety, so it is preferable to an excisional biopsy. It is necessary to avoid inappropriate treatments, such as diathermocoagulation, given the risk of recurrence and diagnostic delay.

Several limitations of this study need to be considered. First, our data are from only two centers, potentially limiting the generalizability of our results. Moreover, given the rarity of the tumor, although this diagnostic study is one of the largest cases in the CMA literature to date, the number of lesions included and non-comparative methodology limit a thorough evaluation of other possible variables and do not allow us a more standardized classification approach.

Conclusions

For the first time in the literature, this study has tried to classify the extreme clinical and dermoscopic polymorphism of angiosar-

coma by describing three peculiar patterns. In clinical practice, these patterns and new dermoscopic parameters described, such as red dots and red-brown islands, could be extremely useful for arriving at an early and accurate diagnosis of this fearful and aggressive tumor. However, further research is needed to validate these patterns in larger cohorts and refine their utility in clinical practice.

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Contributions: Vincenzo De Giorgi: conception and design; Biancamaria Zuccaro, Giovanni Cecchi, Gabriella Perillo: data acquisition; Vincenzo De Giorgi, Giovanni Cecchi: data analysis and interpretation; Vincenzo De Giorgi, Giovanni Cecchi, Piero Covarelli: writing – original draft; Biancamaria Zuccaro, Ignazio Stanganelli, Vincenzo De Giorgi: investigation; Vincenzo De Giorgi: revision; Vincenzo De Giorgi, Piero Covarelli: supervision. All authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors have no relevant conflict of interest to declare.

Ethics approval and consent to participate: no institutional review board review or approval was necessary. The study was conducted in accordance with all legal and regulatory requirements.

Consent for publication: patients gave written informed consent to the publication of their case details and any accompanying images.

Availability of data and materials: the datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.