Cutaneous angiosarcoma: a current update

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ABSTRACT

Cutaneous angiosarcoma (cAS) is a rare malignant neoplasm with variable clinical presentation. Although a distinct vascular tumour, cAS shares many overlapping histopathological features with other vasoformative and epithelioid tumours or ‘mimickers’. cAS shows aggressive behaviour and carries a grave prognosis, thus early diagnosis is of paramount importance to achieve the best possible outcomes. Recently, several genetic studies were conducted leading to the identification of novel molecular targets in the treatment of cAS. Herein, we present a comprehensive review of cAS with discussion of its clinical, histopathological and molecular aspects, the differential diagnosis, as well as current therapies including ongoing clinical trials.

INTRODUCTION

Angiosarcoma (AS) is a rare and highly aggressive malignant neoplasm derived from vascular endothelial cells that has predilection for the skin and superficial soft tissues. The diagnosis of cutaneous AS (cAS) carries a poor prognosis with a high rate of local recurrence and tendency to metastasise despite aggressive therapy. AS can arise sporadically, primarily affecting the head and neck region of elderly individuals, as a consequence of radiation therapy, or in association with chronic lymphoedema (Stewart-Treves syndrome). Despite ongoing clinical trials, treatment options for all three subtypes are limited. Thus, timely and accurate diagnosis of these lesions is essential in order to ensure the most optimal outcome.

The diagnosis of cAS is often delayed due to its subtle initial clinical appearance as it is often mistaken for an ecchymosis or haematoma. In elderly patients on anticoagulants, it may be virtually impossible to discern an early cAS on clinical grounds alone. Histopathologically, cAS may be just as subtle and often mistaken for one of its mimics including: traumatised capillary haemangioma, Kaposi sarcoma (KS), spindle cell haemangioma, atypical vascular lesion (AVL), haemangioendothelioma, melanoma, carcinoma and atypical fibroxanthoma (AFX). The distinction between AS and its mimics is challenging with important clinical implications.

This review aims to describe the clinicohistopathological features of AS and its potential mimickers as well as provide an update on molecular characterisation and emerging therapeutic agents.

AS VARIANTS AND THEIR INCIDENCE

The most common variant of cAS presents on the head and neck (Wilson-Jones type) representing less than 0.1% of all head and neck malignancies. cAS can be a challenging clinical and histological diagnosis. cAS often demonstrates rapid progression and is associated with the highest rate of lymph node metastasis among all soft tissue sarcomas of the head and neck. This variant is seen more frequently in men than women with a ratio of 1.7:1.

Although rare, radiation-associated angiosarcoma (RAA) is the most recognised complication of radiation therapy. Frequently seen in patients treated with breast-conserving therapy for breast carcinoma, RAA has a reported incidence of 0.05%–0.14%.5 6 The latency period between radiation and development of cAS is 2–30 years with a median of 5 years, which is shorter than the development of other radiation-induced neoplasms.5 6 Mery et al reported that the incidence of cAS peaked at 10 years and the risk diminished only after 20 years postradiation.6 Vorburger et al demonstrated a shorter mean latency period (between initiation of radiation therapy and development of AS) of 7.6 years for breast RAA, compared with 20.9 years for RAA arising in other anatomic sites. A study by Hung et al comparing RAA and sporadic AS of the breast showed that 80% of RAA were cutaneous in origin, compared with sporadic AS, of which 80% demonstrated parenchymal origin.8 Interestingly, there appears to be no difference in survival between sporadic AS and RAA of the breast.9

The development of AS in the setting of chronic lymphoedema was initially described in 1948 by Stewart and Treves, representing approximately 5% of AS.10 11 The majority of reported cases are those affecting the upper extremity of patients who have undergone radical mastectomy for locally advanced breast cancer. As a result of the extended latency period, most cases are diagnosed 10–15 years post-treatment. It has been proposed that the accumulation of protein-rich interstitial fluid may alter and compromise the immune response consequently stimulating lymphangiogenesis and growth of collateral vessels.12 This type of AS was also reported in patients with congenital lymphoedema, filariasis and morbid obesity.13 15

Rare cases of metastases from sternal, cardiac and aortic AS are described.16–19 Paediatric AS is uncommon and is usually associated with radiation therapy or underlying genetic abnormalities, such as xeroderma pigmentosum, Aicardi syndrome and congenital lymphoedema.20–22 Malignant transformation of infantile haemangioma into AS has been reported.23

AETIOLOGY AND MOLECULAR CHARACTERISTICS

Multiple aetiological factors may play a role in cAS, including lymphostasis, radiation and chronic sun...
exposure. cAS has been described in patients with xeroderma pigmentosum, as well as in immunocompromised patients with HIV and postrenal transplantation. Neoplasms developing in fistulas for haemodialysis in immunocompetent patients have been described, indicating that abnormalities in vascular flow may cause neovasculogenesis. In addition, cases of AS arising in association with implantation of foreign material have been reported.

cAS is a genetically complex neoplasm with mutations in several pathways, involving the most common genes such as TP53, KRAS, PTPRB and PLCG1. A mutation in the TP53 gene, responsible for tumour suppressor protein p53 synthesis, is one of the most common mutations in cancer. While some studies suggest that TP53 mutations are seen in more than half of AS cases, others report that the incidence of TP53 mutations in AS is actually lower than in other soft tissue sarcomas. The PTPRB (a negative regulator of vascular growth tyrosine kinase) and PLCG1 (signal transducer of tyrosine kinase) genes play an important role in activating angiogenesis and are the most specific for AS likely functioning as driver mutations. A mutation in the UNC5A gene, recently identified in 9 of 25 AS and may play a role in regulating other genes involved in angiogenesis.

Recently, a novel fusion gene, NUP160-SCL43A3, was identified in 9 of 25 AS and may play a role in regulating other genes involved in angiogenesis.

Primary and secondary cAS have different molecular profiles. The upregulation of MYC, KIT, FLT4 and RET genes and down-regulation of CDKN2C were reported in radiation-induced (secondary) cAS. Upregulation of additional genes including UNCSA, CTLA4, ISL2, ICOS, RAB17, FLT4 and RASGRP3 has also been identified in secondary cAS, while NTSR-1, ANKRD1 and CDKN2C were shown to be associated with primary cAS. KDR mutations were found to be associated with primary and secondary cAS of the breast.

**CLINICAL FEATURES**

AS most frequently affects the face, scalp and neck of elderly individuals, and men are affected more than women. Clinically, AS presents asymptomatically as a haematoma-like lesion, but may also resemble rosacea, eczema, haemangioma, violaceous plaques or nodules, xanthelasma, cellulitis, and facial and eyelid angioedema. Nodules, papules, plaques and exophytic tumours develop on the surface of progressing lesions. Not uncommonly, advanced lesions can mimic epithelial neoplasms including squamous cell carcinoma, keratoacanthoma, basal cell carcinoma, AFx and malignant melanoma. Often the lesions of AS are multifocal and extend beyond the clinically identifiable borders of the lesion(s). Thus, determination of the extent of disease is often challenging. On physical examination, tilting the head may increase blood supply to the lesion and assist with visualisation of the tumour. Symptomatic thrombocytopenia (Kasabach-Merritt syndrome) is a rare, but recognised complication of AS and may be a potential diagnostic clue when evaluating physical findings and complete blood counts.

**HISTOPATHOLOGICAL FEATURES**

cAS is highly variable morphologically. The well-differentiated lesions are typically characterised by irregular, anastomosing and dilated vascular structures with largely inconspicuous endothelial cells and may be misinterpreted as haemangioma or lymphangioma, particularly in a superficial biopsy specimen. Architecturally, the irregular vessels dissect the underlying dermis forming a network. On higher magnification, malignant endothelial cells appear pleomorphic and hyperchromatic and often bulge into vascular lumina (figure 1A,B). Poorly differentiated cAS can form sheets of mitotically active, pleomorphic cells with ill-defined, intervening vascular structures, which are difficult to distinguish from carcinoma and melanoma (figure 2A–C). The presence of irregular vessels at the periphery of the tumour, intracytoplasmic vacuoles, small areas of haemorrhage and erythrocytes in vascular lumens may serve as diagnostic clues for vascular origin.

Epithelioid cAS is a variant characterised by the predominance of round or polygonal cells with abundant eosinophilic cytoplasm and vesicular nuclei. Nodular, micronodular, syncytial and diffuse growth patterns have also been described (figure 3A,B). Zones of necrosis are often observed.

Other rare cytological variants include clear-cell, foam-cell, signet-ring and granular-cell changes. Cases of cAS with hypertrophic and papillomatous changes have been described as verrucous cAS. There are rare cases of ‘pseudo-lymphomatous AS’ with heavy inflammatory infiltrates, and variable germinal centre formation has been reported.

**IMMUNOHISTOCHEMISTRY AND HISTOPATHOLOGICAL PROGNOSTIC FEATURES**

CD31 and CD34, both cytoplasmic, are the most frequently used immunohistochemical markers for the diagnosis of cAS. However, these markers are widely expressed by other cell

![Figure 1](image-url)
CD34 may be expressed in haematopoietic and fibrohistiocytic cells. CD31 is more specific, but may also be expressed in macrophages, histiocytes and plasma cells, leading to possible diagnostic pitfalls. Nuclear immunohistochemical markers, including ERG (Avian v-ets erythroblastoasis virus E26 oncogene homologue) and FLI1, from the ETS transcription family, are thought to be highly sensitive for cAS\(^52\)\(^56\)\(^57\) (figure 2B). Despite its sensitivity in AS, FLI1 expression can also be found in leiomyosarcoma, squamous cell carcinoma, melanoma and AFX, making it a less optimal choice when these neoplasms are within the differential. Claudin-5, a tight junction protein, is another sensitive vascular marker and may be helpful if additional confirmation of vascular origin is necessary. Demonstrating positive expression in the majority of cAS, Claudin-5 lacks specificity as it is also expressed by other vascular proliferations.\(^58\)

Less frequently used vascular markers include von Willebrand factor, BNH9, factor VIII-related antigen, PROX-1 and Ulex europaeus (a lectin that stains endothelium and epithelium). In addition, cAS expresses lymphatic markers D2-40 and VEGFR-3. In contrast to conventional cAS, epithelioid AS may express cytokeratins and epithelial membrane antigen (EMA).\(^59\) CD30 expression has also been reported in one case of postradiation cAS with epithelioid morphology.\(^60\)

The anti-c-MYC antibody is expressed by secondary cAS and is most helpful in distinguishing these tumours from AVLs of the breast that may arise secondary to therapeutic radiation for breast cancer.\(^61\) Harker et al showed MYC nuclear expression by immunohistochemistry and amplification by fluorescence in situ hybridisation (FISH) in two cases of secondary cAS arising in obese patients with lymphostasis.\(^62\) Shon et al showed that 23
of 38 primary cAS expressed MYC by immunohistochemistry or FISH, but the significance of this finding is unknown and does not correlate with overall survival.63

Some immunohistochemical features may have prognostic value. Recently, CD98, a marker frequently expressed by cancer cells, was identified in cAS. The presence of CD98 expression in cAS correlated with a worse prognosis.64 Fujii et al reported that patients with a diagnosis of cAS have higher levels of CD8-positive T lymphocytes and demonstrated that tumours with a higher density of tumour-infiltrating lymphocytes tended to have a longer metastasis-free interval.65

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of cAS includes multiple entities and highly depends on the tumour variant and its cellular morphology. cAS should first be differentiated from the group of benign and malignant vascular proliferations. cAS of the breast is most frequently misdiagnosed as AVL of the breast. AVL of the breast appears as a skin-coloured vesicle or papule, ranging from 1 to 20 mm in diameter, and usually develops 3 years postradiation or surgery. Distinguishing AVL from AS may be extremely challenging as cAS may show focal overlapping features of AVL in small or superficial biopsies. AVLs may form irregular vessels, which may appear thin and dilated in the lymphatic type and normal in the vascular type. Although possible, AVLs typically do not involve the subcutis or display irregular staghorn architecture. Usually, the absence of necrosis, atypical endothelial mitotic figures and areas of haemorrhage are helpful findings.66-68 (figure 4).

Other benign vascular hyperplasias and neoplasms that may be occasionally mistaken for cAS include: angiolymphoid hyperplasia with eosinophilia, verruca peruana, cutaneous epithelioid angiomatous nodule, glomeruloid haemangioma, tufted haemangioma, infantile haemangiomas, intravascular papillary epithelial hyperplasia, targetoid haemosiderotic haemangioma, progressive lymphangioma, pyogenic granuloma, sinusoidal haemangioma and spindle cell haemangioma.69-74 There are no reliable immunohistochemical markers helpful in the differentiation of cAS from benign vascular proliferations. The diagnosis relies primarily on the clinical presentation, history and microscopic features. Usually, cellular atypia, mitotic figures and necrosis are not seen in benign vascular neoplasms or are present only focially, and in association with inflammation, ulceration or trauma.

Malignant and borderline vascular neoplasms potentially mimicking cAS include KS and haemangioendotheliomas including: composite haemangioendothelioma, epithelioid haemangioendothelioma (EHE), kaposiform haemangioendothelioma (KHE), papillary intralymphatic angioendothelioma (PILA) and retiform haemangioendothelioma (RHE).

The histopathological features of KS and cAS may be very similar. Both neoplasms form slit-like vascular structures and may demonstrate spindle cell morphology. The characteristic promontory sign (blood vessels protruding into an abnormal vascular space), although often seen in KS, is not specific and has been described in a variety of benign vascular proliferations and may be focally observed in cAS.75-77 Nuclear atypia is usually less prominent in KS, unlike in cAS. Nuclear expression of HHV-8 by immunohistochemistry is seen in KS but not cAS77,78 (figure 5A–C).

Composite haemangioendothelioma is a rare, locally aggressive but slowly growing malignant tumour, which usually presents as dermal or subcutaneous nodules or plaques on the hands and feet of adults. The distinguishing microscopic finding is the combination of patterns within the same tumour (EHE, RHE, spindle cell haemangioma, AS-like and benign lymphatic or vascular areas). EHE and RHE patterns usually predominate.79 AS-like areas of composite haemangiopithelioma may mimic low-grade, classic AS and the diagnosis is often difficult in small biopsies.80

EHE is an angiocentric vascular tumour that most frequently involves soft tissue, bone and solid organs. Although initially thought to represent a low-grade malignancy, EHE has significant metastatic potential with reported rates ranging from 20% to 30%. Primary cutaneous variants are rare and show more indolent behaviour with only one reported case of lymph node metastasis described in the literature.81 EHE characteristically expands the vessel wall, occludes the lumen and spreads into surrounding tissue. Histologically, the neoplasm demonstrates cords, strands and solid aggregates of bland epithelioid cells with little or no mitotic activity (figure 6A–C). Cytologically, there are intracytoplasmic vacuoles containing erythrocytes, thus supporting endothelial differentiation. The cells are typically enveloped by a myxohyaline, sulphate-rich stroma.82 An identical translocation of chromosomes 1 and 3 [t1;3 (p36;q23-25)] resulting in a WWTR1-CAMTA1 fusion is considered diagnostic of this entity.83

KHE occurs almost exclusively in young children and has a predilection for the extremities.84 It shares histopathological features with tufted haemangioma (infiltrating tufts of capillaries in a characteristic ‘cannonball’ pattern). Unlike tufted haemangioma, KHE primarily involves the subcutis, retroperitoneum, may invade internal organs and is characterised by aggressive growth. KHE may potentially be associated with the Kasabach-Merritt phenomenon.

PILA, also recognised as Dabska tumour, is characterised by an extensive proliferation of lymphatic channels with intralymphatic papillary projections consisting of hyaline cores and ‘hobnail’ endothelial cells.85 Features distinguishing this tumour from the classic variant of AS include the lack of cytological atypia and only rare mitotic activity.

RHE is locally aggressive and has a high recurrence rate. It is often classified as a low-grade malignancy, with only one case reported as having lymph node metastasis.86 RHE is characterised by elongated and narrow arborising vascular channels that resemble the rete testes. Unlike in cAS, the endothelial cells in

Figure 4 Atypical vascular lesion: proliferation of slightly irregular vessels with no atypia (H&E, 20×).
RHE are monomorphic. The endothelial cells lining vascular channels have a ‘tombstone’ or ‘hobnail’ appearance. By immunohistochemistry, RHE is similar to cAS. The cells express CD31, CD34 and ERG, but are usually negative for D2-40 and VEGFR-3.

Figure 5  (A) Kaposi sarcoma: vascular proliferation comprising irregular vessels with ‘promontory sign’ (H&E, 10×). (B) Higher magnification of Kaposi sarcoma: irregular vessels with less atypia compared with cutaneous angiosarcoma (H&E, 20×). (C) Kaposi sarcoma: an immunohistochemical study for HHV-8 highlights endothelial cell nuclei (IHC, 20×).

Figure 6  Epithelioid haemangioendothelioma (A: low magnification, B: high magnification): cords, strands and solid aggregates of epithelioid cells with admixed erythrocytes embedded in a background of myxohyaline stroma. (C) ERG demonstrating nuclear expression of endothelial cells supporting endothelial differentiation.

Poorly differentiated cAS, particularly tumours with spindle cell morphology and those with solid growth, should be differentiated from other epithelial and soft tissue neoplasms including AFX, leiomyosarcoma, undifferentiated squamous cell carcinoma, adenocarcinoma and spindle cell melanoma. Immunohistochemistry is often necessary. While the expression of vimentin...
and desmin is supportive of leiomyosarcoma, squamous cell carcinomas express p63, p40, and cytokeratin, and EMA positivity is observed in squamous cell carcinomas. A combination of melanocytic markers including SOX10, S100, MITF and melan-A is helpful in the diagnosis of melanoma. AFX is a diagnosis of exclusion and sometimes presents great difficulty. Similar to the preferred anatomic location in cAS, AFX typically presents on the head of elderly patients and is sometimes clinically mistaken for cAS. The expression of CD31 and ERG is the most helpful in distinguishing the two entities and highly supports cAS.88

The histological differential for cAS with epithelioid features may include epithelioid sarcoma, presenting a challenge if the diagnosis is based on histopathological grounds alone. Epithelioid sarcoma has been shown to express ERG, FLI1, CD34 as well as D2-40.89 However, the anatomic location (predilection lower extremities) demonstrates multifocality, and generally supports the diagnosis of epithelioid sarcoma.91

Epithelioid sarcoma-like haemangioendothelioma is another entity which may be included in the differential diagnosis of epithelioid cAS. This rare vascular neoplasm has both epithelioid and spindle cells with minimal atypia which resemble both epithelioid and myogenic proliferations. Pseudomyogenic haemangioendothelioma usually develops in young men in the lower extremities, demonstrates multifocality, and generally a benign clinical course, though rare cases have been reported to show aggressive behaviour and metastases.92 This entity expresses cytokeratin AE1/AE3, ERG, vimentin, FLI1 and CD31, but lacks expression of CD34.92,93 Recently, an associated chromosomal translocation t(7;19)(q22;q13) was discovered leading to SERPINE-FOSB gene fusion. In addition, immunohistochemistry with FOSB is highly specific for this neoplasm.94,95

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STAGING AND PROGNOSIS
The American Joint Committee on Cancer and the International Union Against Cancer grading systems are not applicable to cAS, and histopathological grading system is not prognostic for cAS. In a case series of 69 sporadic cAS, Deyrup et al found that the presence of epithelioid morphology and necrosis is associated with worse prognosis.96 They proposed to subdivide cAS into two categories: low risk and high risk. They found that by using these criteria to stratify tumours into one of these two categories, the patients in the high-risk group did not survive longer than 5 years.96 In contrast, Dettenborn et al reported no association between survival and the presence of epithelioid morphology and/or necrosis, but found that 80% solid tumour growth pattern is associated with better prognosis.7

Prognosis in cAS is poor with median survival about 3.4–5 years.97,99 To date, the largest data on survival of patients with cAS were collected by the National Cancer Institute’s Surveillance, Epidemiology, and End Results programme, and 434 cases of cAS were analysed.98 Age was a significant factor with only 36.8% 10 years survival of patients older than 50 years.96 Several factors including age over 50, male sex, the presence of cardiovascular disease, history of smoking, location in the scalp, tumour size over 5 cm, presence of satellites at the time of diagnosis and treatment without adjuvant chemotherapy may serve as predictors for poor prognosis.97,99 The rate of local recurrence is high and may reach 63%.97 Distant metastases develop in up to 36% of patients.97 They often develop in less than 1 month after primary tumour with the average time of 1 year.97 The lungs are the most common site for distal metastasis of cAS, followed by bone and liver.97

CURRENT TREATMENT RECOMMENDATIONS AND UNDERGOING CLINICAL TRIALS
Currently, combination of surgery and radiation is the mainstay of treatment for cAS. A study performed at the University of Texas MD Anderson Cancer Center demonstrated that patients who undergo combination therapy have statistically greater overall survival compared with those who undergo radiation or surgery alone.97 Histopathologically clear surgical margins are of paramount importance and correlate with better outcome.100 Although no clear guidelines exist on the specific width of surgical margins in cAS, achievement of 3 cm or greater clear margins as well as deep margins is recommended.5

Data regarding chemotherapy in cAS are inconsistent. While some studies show benefits of adjuvant chemotherapy, others report no increase in overall survival.2,97,99 At the same time, chemotherapy is widely used in metastatic cAS and lesions that cannot be entirely resected.101 Doxorubicin-based regimens are considered to be the gold standard for treatment of soft tissue sarcomas with a reported progression-free survival (PFS) lasting approximately 3 months in different studies.102–104 Therapy with taxanes (paclitaxel) has shown better efficacy compared with doxorubicin with a median PFS of 4–5 months.102–104

Tyrosine kinase inhibitors (pa pazopanib, sorafenib, axitinib) are used to treat various soft tissue sarcomas including cAS. Studies evaluating pazopanib have shown conflicting results. Kollar et al reported that pazopanib had similar efficacy in treating AS compared with other soft tissue sarcomas with a PFS of 3 months.105 In contrast, Kitamura et al found no differences between the pazopanib-treated group and the control group.106 Therapy modalities, targeting vascular proliferation, are currently under investigation (table 1). Bevacizumab, a VEGFR inhibitor, was reported to be an effective treatment option for AS with a PFS of 6.5 months.107 Combinations of bevacizumab and paclitaxel are under investigation. Other potential therapies include carotuximab, a monoclonal antibody to endoglin, and regorafenib, a dual inhibitor of VEGFR2-TIE2 tyrosine kinase. In 12 of 16 patients treated with trabaniib, which targets angiotensin 1 and 2, no response was reported and the study was closed.108 A summary of clinical trials registered at clinicaltrials.gov (accessed 15 March 2017) is given in table 1.

Expression of the beta-adrenergic receptor in vascular tumours and successful management of infantile haemangiommas with oral and topical beta blockers led to the consideration and investigation of propranolol in AS. Stiles et al showed that selective blockade of beta-adrenergic receptors led to the apoptosis and inhibition of vascular proliferation in vitro and in vivo.109 The addition of propranolol to the chemotherapy regimen has shown promising response in several case reports.110–112

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