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Original Contributions

Primary and secondary cutaneous angiosarcoma: Distinctive clinical, pathological and molecular features

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ABSTRACT

Angiosarcomas are ubiquitous neoplasms involving both cutaneous and soft tissue and visceral locations. Accumulating biomolecular evidences suggest that cutaneous angiosarcomas are distinctive entities with molecular, clinical and pathological peculiarities. Despite several ongoing clinical trials with promising therapeutic agents, the prognosis of cutaneous angiosarcomas is dismal and survival still rely on early diagnosis and surgery. An accurate diagnosis and the knowledge of the underlying molecular landscape are therefore essential to improve the prognosis. We detail the molecular, clinical, dermoscopic, morphological and prognostic features of cutaneous angiosarcoma. Although the molecular landscape of cutaneous angiosarcoma is not completely understood, accumulating evidences suggest that there are characteristic molecular alterations including dysregulation of angiogenesis and several complex molecular pathways. Secondary cutaneous angiosarcomas, arising in correlation with chronic lymphedema and ionizing radiation, have different molecular hallmarks, which are also leading to the first diagnostic applications. The diagnosis of cutaneous angiosarcoma may be challenging, as well-differentiated forms can be hard to distinguish from benign and low-grade vascular neoplasms, while poorly differentiated forms can be easily confounded with other non-vascular high-grade neoplasms. An accurate and early diagnosis, which is mandatory to ensure the best survival for the patients, is mainly based on morphological hallmarks.

1. Introduction

Angiosarcomas (ASs) are a heterogenous group of malignant neoplasms characterized by endothelial differentiation [1]. ASs are ubiquitous neoplasms, involving both visceral and cutaneous and soft tissue locations. Rarely, they occur in association with other neoplasms [2]. Cutaneous angiosarcomas (cASs) are highly aggressive tumours arising in the skin, mainly seen in elderly patients with chronic solar damage, lymphedema or history of ionizing radiation [3]. Molecular findings in cASs partially differ from those occurring in visceral ASs. Despite several ongoing clinical trials with promising therapeutic agents, the prognosis of cASs is dismal and currently available treatment options are still limited. Consequently, an accurate and early diagnosis is essential for the best management of the patient. However, cASs are heterogeneous in terms of clinical presentation and histomorphology, and the differential diagnosis is wide, including benign vascular neoplasms, vascular tumours of uncertain malignant potential and high-grade neoplasms with differentiation other than endothelial.

This review aims to describe the biological, molecular, clinical and histolopathological features of cASs, with particular reference to the tools for correct recognition of these tumours and recently introduced diagnostic and prognostic factors.

2. Epidemiology and localizations

Cutaneous angiosarcoma (cAS) is a rare neoplasm with an incidence rate of about 0.5 new cases per 1,000,000 persons per year in the United States according to the Surveillance, Epidemiology, and End

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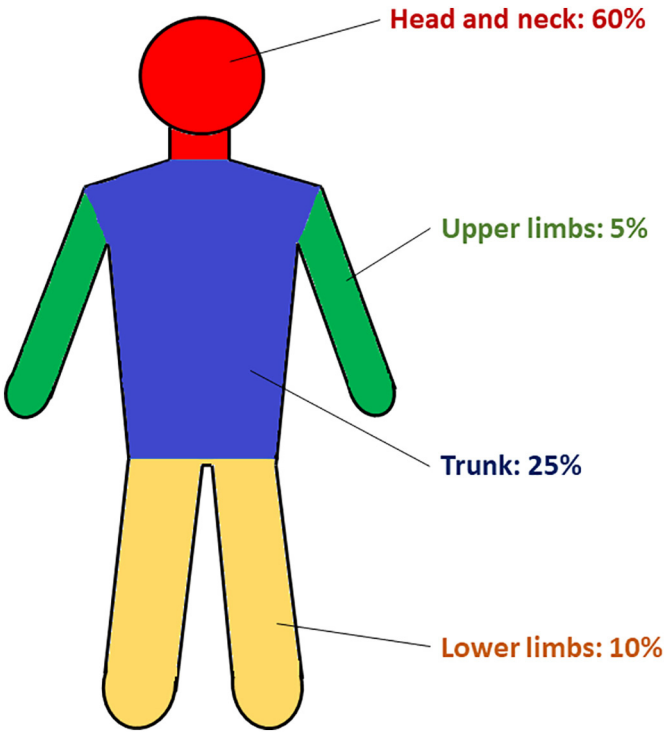

Fig. 1. Anatomical distribution of cutaneous angiosarcoma.

Results (SEER) Program database, accounting for less than 1% of all cutaneous sarcomas [4]. Currently the incidence rate seems to be increased in people over the age of 70 years, supposedly due to the relatively wide application of radiation-based therapies and the long-standing solar exposure in this age group [5]. Indeed, up to 85% of cAS cases occurs in patients older than 60 years, and 65% in patients older than 70 years of age [5]. Overall, the head and neck region is the most commonly affected site for cAS, accounting for approximately 60% of all cases, with some geographic variability. In fact, head and neck location seems to be even more frequent in Asian as compared to Western countries, being more than 95% of all cASs in some Asian series [6]. Other sites, in order of frequency, include the trunk (25% of all cases), the lower limbs (10% of all cases) and the upper limbs (5% of all cases) [6] (Fig. 1). Radiation-associated cASs more commonly arise on the trunk, while lymphedema-associated cASs are more often localized on the extremities [7]. cAS is extremely rare in paediatric age. cASs occasionally reported in children tend to be small and unifocal, located on the lower extremities [8].

3. Etiology and molecular biology

3.1. Cutaneous AS molecular landscape: peculiarities with respect to visceral AS

Overall, the genetic profile of cAS is complex and not well defined, but the current knowledge suggests that ASs harbour biological differences by the site and that cAS may have biological peculiarities. The most commonly mutated genes in cAS include *TP53*, *KRAS*, *PTPRB* and *PLCG1* [9]. Primary cAS frequently shows alterations of *NTSR-1*, *ANKRD1* and *CDKN2C*, while upregulation of *MYC*, *KIT*, *FLT4*, *RET*, *UNC5A*, *CTLA4*, *ISLR2*, *ICOS*, *RAB17*, *FLT4* and *RASGRP3* has been reported in secondary cAS [10,11]. Dysregulation of angiogenesis is one of the major molecular events in cAS. Indeed, an increased expression of both angiogenic tyrosine kinase receptors, including VEGFR1/2/3, and angiogenic growth factors, including VEGF, has been demonstrated in AS [12]. Furthermore, several other angiogenesis-related genes are frequently altered and upregulated in AS, including *VEGFR2/KDR*, phospholipase C gamma 1 (*PLCG1*) and vascular endothelial-protein tyrosine phosphatase (*VE-PTP*) [13,14]. Panse et al. have recently reported decreased expression of *NOTCH1*, a component of the Notch signalling pathway normally expressed by endothelial cells, in a subset of AS, in association with skin location [15].

4. Primary versus secondary cASs: two different biomolecular profiles

The etiology and pathogenesis of cAS are still poorly understood. According to evidences accumulated during the last decades, two types of cAS can be defined on a pathogenetic basis: primary cAS, arising *de-novo* in a chronically sun-damaged skin, and secondary cAS, occurring mainly in a context of chronic lymphedema or in irradiated skin [3]. Although lymphedema and ionizing radiations are the most frequent and well-characterized clinical conditions associated with the development of secondary cAS, correlations also with xeroderma pigmentosum, immunodepression (AIDS, postrenal transplantation), implantation of foreign material and fistulas for haemodialysis have also been described [16-19]. These observations seem to suggest that a chronic skin damage, abnormalities in vascular flow and immune impairment underlie the development of cAS, probably through the activation of neovasculogenesis [20]. The pathogenetic association between chronic lymphedema and the development of cAS are still largely unexplained. Microenvironmental immune alterations determined by ineffective lymph drainage seem to play a role, causing dysfunctions in antigen-presenting dendritic cells and cytotoxic T lymphocytes and triggering vascular proliferation. Several cytokines and growth factors are involved in this process. For example, increased levels of IL-10, an immunomodulatory cytokine hindering the recruitment of macrophages and delaying wound healing, have been demonstrated in lymphedema [21]. A percentage of cASs is characterized by activation of *MYC*, by gene amplification or protein overexpression (Fig. 2). *MYC* is a proto-oncogene located on chromosome 8q24 involved in several complex cellular pathways with effects on cellular proliferation, differentiation, apoptosis and angiogenesis [22]. The first studies demonstrated *MYC* activation only in secondary cAS, suggesting different pathogenetic mechanisms for primary and secondary cASs [10,23,24]. However, although considered distinctive for secondary cASs, most recent studies have identified the presence of MYC activation also in a subset of primary cASs. Shon et al. have evaluated *MYC* status in a series of 38 primary cASs, demonstrating *MYC* overexpression by immunohistochemistry in 24% of cases; *MYC* amplification by fluorescence in situ hybridization (FISH) (MYC:CEP8 ratio ≥ 2) in 17.4% of cases; polysomy of chromosome 8 without MYC amplification in 48% of cases [25]. Nevertheless, Myc protein overexpression seem to be at least partially independent from *MYC* gene amplification and a role for other regulatory factors and genes is conceivable. Similarly, the clinical implications of *MYC* abnormalities in cAS are not well defined. In particular, they were seen to correlate with the clinical behavior of the neoplasm in some studies [26] but not in others [10,25].

5. Clinical findings and dermoscopy

Clinical features of cASs are extremely variable, since the neoplasm may mimic both other cutaneous neoplasms and non-neoplastic skin diseases. For example, cases of cASs clinically simulating rosacea, eczema, haemangioma, xanthelasma, cellulitis, and facial and eyelid angioedema, squamous cell carcinoma, keratoacanthoma, basal cell carcinoma, atypical fibroxanthoma and malignant melanoma have been reported in literature [27-29]. However, at least in early stages, the most common presentation is that of a haematoma-like lesion (Fig. 3). In more advanced stages, nodules, papules and plaques may develop. A symptomatic thrombocytopenia is rarely associated to cAS (Kasabach-Merritt syndrome). The dermatoscopic features of angiosarcoma are not clearly defined. The few published works on the topic describe, among

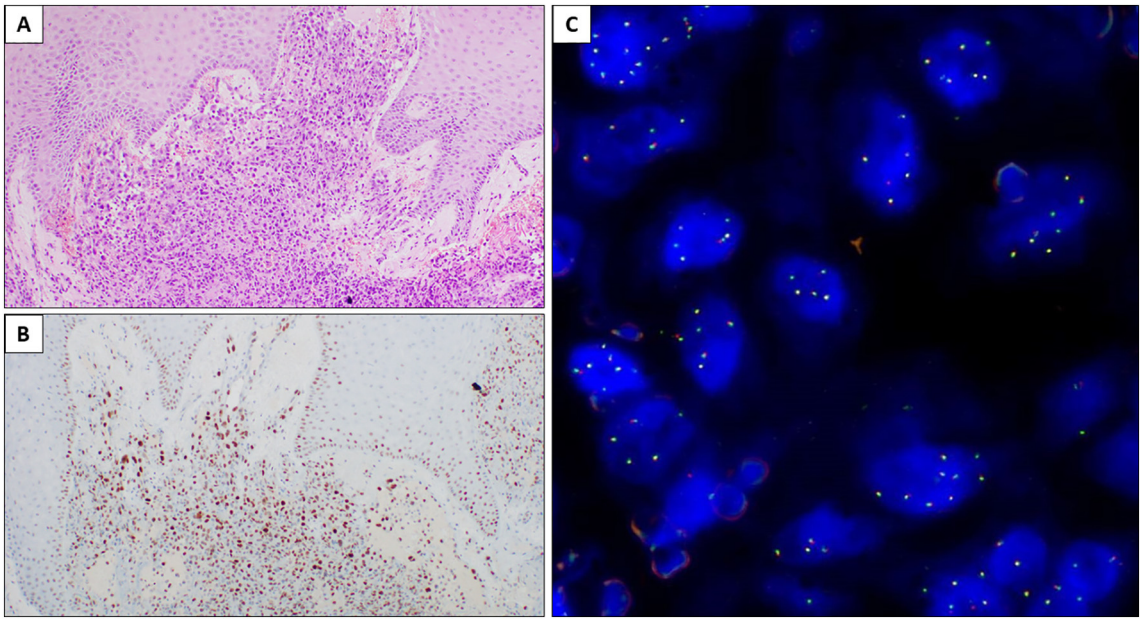

Fig. 2. A case of secondary cAS. A) A solid population of epithelioid cells in the dermis (H&E, original magnification 100×). B) Neoplastic cells showing expression of Myc protein (immunohistochemical stain, original magnification 100×). C) Fluorescence in situ hybridization (FISH) showing amplification of MYC gene.

recurrent findings, structureless red to purple or purple to bluish areas including yellowish clods, purple globules and 'hypopyon' sign [30-32].

6. Histological findings

Histologically, cASs are quite heterogenous, depending on the degree of differentiation. Well-differentiated cASs display readily apparent vascular formation, while poorly differentiated cASs may show only limited – if any – morphological evidence of vascular differentiation. The diagnosis of cAS may be challenging, as well-differentiated forms can be hard to distinguish from benign and low-grade vascular neoplasms, while high-grade cASs can be easily confounded with other non-vascular poorly differentiated neoplasms (carcinomas, melanomas, sarcomas). The main entities entering the differential

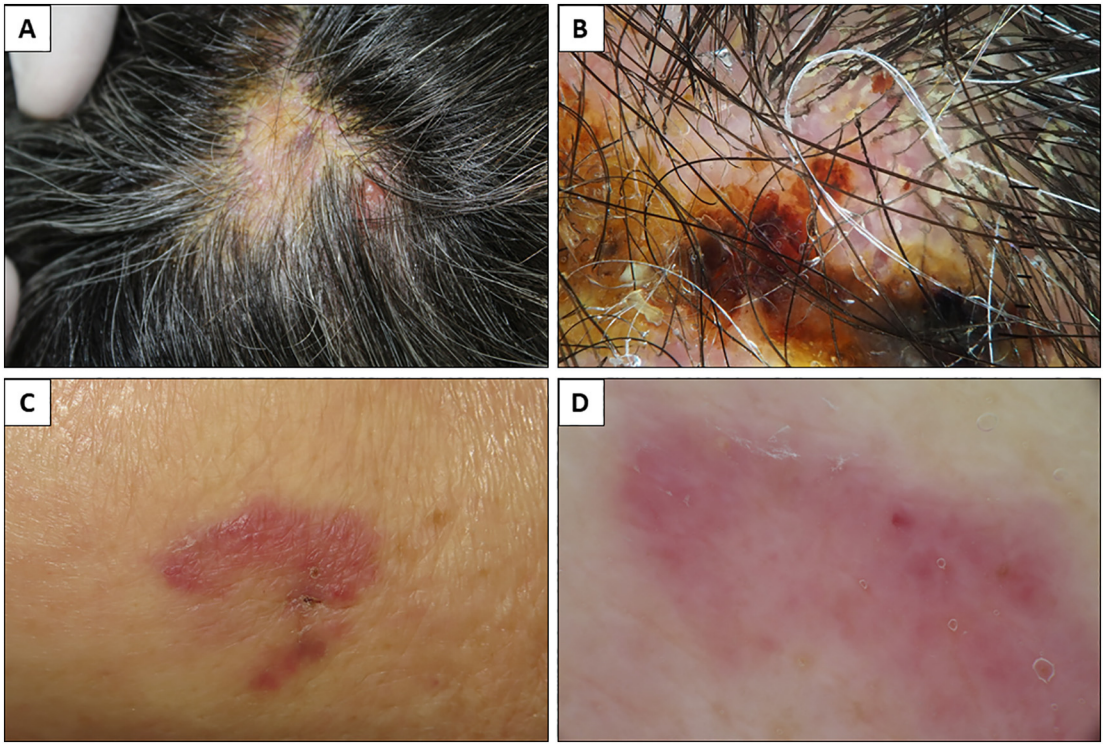

Fig. 3. Clinical and dermoscopic findings. A-B) Primary cAS. A) An erythematous plaque arising on the scalp of a 50-year old woman. The lesion was present since few months, mainly as a flat purple area of the vertex, lately developing a nodular amelanotic component. B) No specific features could be highlighted on dermoscopy, that revealed a pink to purple structureless area and superficial scaling. Secondary cAS. C-D) Secondary cAS. C) A pink plaque arising on the trunk of a 75-year old woman, treated with radiation therapy for breast cancer 10 years before. D) On dermoscopy a pink structureless area is visible with few reddish lacunes. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Differential diagnosis of cutaneous angiosarcoma.

Entity	Age and location	Clinical findings	Histological findings	Immunohistochemical findings
Well-differentiated cutaneous angiosarcoma				
Glomeruloid hemangioma	Any age; trunk and limbs.	multiple and eruptive red or purple papules; possibly associated with Castleman's disease or POEMS syndrome.	Dermis; grape-like pattern (lobular and sinusoidal dermal vascular aggregates); small capillary-type vessels.	Endothelial markers
MIcrovenular hemangioma	Young to middle-aged adults; forearms, trunk, limbs.	Single slow-growing red or purple papule.	Dermis; pseudoinfiltrative pattern of growth; thin-walled vessels; collapsed lumina; possibly myxoid stroma; plumper endothelial cells.	Endothelial markers
Targetoid hemosiderotic hemangioma (hobnail hemangioma)	Young to middle-aged adults; trunk, limbs.	Red or purple papule surrounded by clear and brown ring (targetoid appearance).	Dermis; pseudoinfiltrative pattern of growth; dilated or serpiginous thin-walled vessels; hobnail endothelial cells; fibrin thrombi; hemosiderina.	Endothelial markers
Spindle cell hemangioendothelioma	Children to young adults; extremities.	Multiple red-bluish nodules; possibly associated with Maffucci's syndrome and Klippel-Trenaunay syndrome.	Dermis and subcutis; solid pattern of growth with slit-like lumina; spindle-cells; cavernous vessels; plump endothelial cells.	Endothelial markers
Angiolymhpoid hyperplasia with eosinophilia	Young to middle-aged adults; head, mainly periauricular areas, forehead and scalp.	Multiple pink, red or brown papules and nodules; may be symptomatic (pruritic, painful).	Dermis; small thin-walled vessels with open lumina; abundant stroma with extensive lymphoid population and eosinophils; possibly hobnail endothelial cells.	Endothelial markers
Reactive angioendotheliomatosis	Middle-aged adults to elderly; ubiquitously.	Multiple red-bluish plaques; possibly ulcerations; possibly associated with chronic infections or arterio-venous fistulae	Dermis; diffuse (seven cases), lobular (six cases), or mixed pattern of growth; slit-like lumina; fibrin microthrombi.	Endothelial markers
Acroangiodermatitis	Middle-aged adults to elderly. Lower extremities;	Multiple purple papules and nodules; inflammatory background. Associated with venous stasis (venous insufficiency, amputation, paralysis).	Dermis; capillary-type vessels; fibroblastic proliferation; edema; hemosiderin; pleump endothelium.	Endothelial markers
Kaposi's sarcoma	Middle-aged adults to elderly. Extremities (classic form); ubiquitously (endemic form and immunosuppressed patients); mucosae, trunk, head and neck, arms, internal organs (HIV-associated form).	Brown or red macules, then bluish or purple patches and nodules.	Dermis, the dermis and hypodermis. In initial phase, angioma-like vascular proliferation; promontory-sign; intravascular pink amorphous globules. In advanced phase: sarcomatous spindle cell proliferation; slit-like vessels; extravasated erythrocytes; hemosiderin; atypia and mitoses.	Endothelial markers, HHV8.
Poorly-differentiated cutaneous angiosarcoma				
Poorly-differentiated squamous cell carcinoma	Middle-aged adults to elderly. Exposed skin, mainly head and neck and extremities.	Firm, red nodule; shallow ulcer; greyish plaque.	Solid pattern of growth; epithelioid or spindle-shaped cells; atypia and mitoses. Connection with epidermis.	CK, EMA, p63, p40.
Pseudovascular squamous cell carcinoma	Middle-aged adults to elderly. Exposed skin.	Ulcer; crusted nodule.	Similar to poorly differentiated squamous cell carcinoma, with presence of pseudovascular lumina lined by tumour cells.	CK, EMA, p63, p40.
Lymphoepithelioma-like carcinoma	Middle-aged adults to elderly. Head and neck.	Greyish nodule or papule.	Abundant lymphoid infiltrate; often lobular pattern of growth; large polyhedral tumour cells with slightly eosinophilic cytoplasm.	CK, EMA, p63, p40.
Atypical fibroxanthoma	Elderly. Exposed skin, mainly head and neck.	Well-demarked, greyish to red nodule.	Dermis. Well-circumscribed; spindle cells, large polyhedral cells, multinucleated giant cells. Atypia and mitoses.	CD10, CD68, CD99, CD74; α1-antitrypsin.
Malignant melanoma	Middle-aged adults to elderly. Exposed skin.	Variable. Pink to brown-black flat of nodular lesions.	Epithelioid or spindle cell; variable amount of pigment; atypia and mitoses.	S100, SOX10, Mart1, HMB45.
Leiomyosarcoma	Elderly. Head and neck, extremities.	Solitary erythematous nodule.	Dermis. Spindle cells; slightly eosinophilic cytoplasm; perinuclear vacuoles; atypia and mitoses.	SMA, MSA.

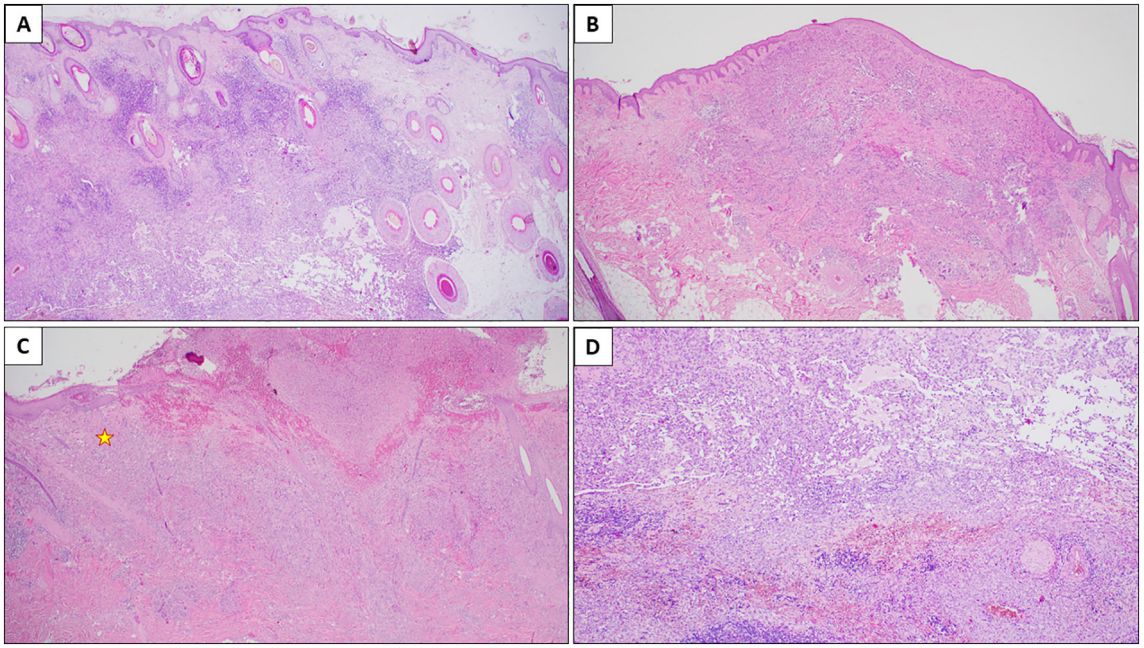

Fig. 4. Pattern of growth of cAS. A) A case of cAS of the scalp. The neoplasm fills the dermis and hypodermis, infiltrating around the hair follicles. The pattern of growth may be different in the the same neoplasm. In this example, the architectural pattern is almost solid in the upper part, while empty vascular lumina are more obvious in the lower part of the neoplasm (H&E, original magnification 20×). B) A case of cAS of the neck. The neoplasm shows poorly defined borders, infiltrating the surrounding dermis (H&E, original magnification ×20). C) A case of cAS of the leg. The neoplasm shows a spindle cell morphology, and some slot-like vascular lumina (yellow star). The epidermis is extensively ulcerated and large hemorrhages are present in the upper dermis (H&E, original magnification 20×). D) A case of cAS of the neck. The neoplasm shows an obvious vascular pattern, as many empty irregular anastomizing vascular channels are evident. Hemorrhages are present in the lower part of the neoplasm (H&E, original magnification 40×). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

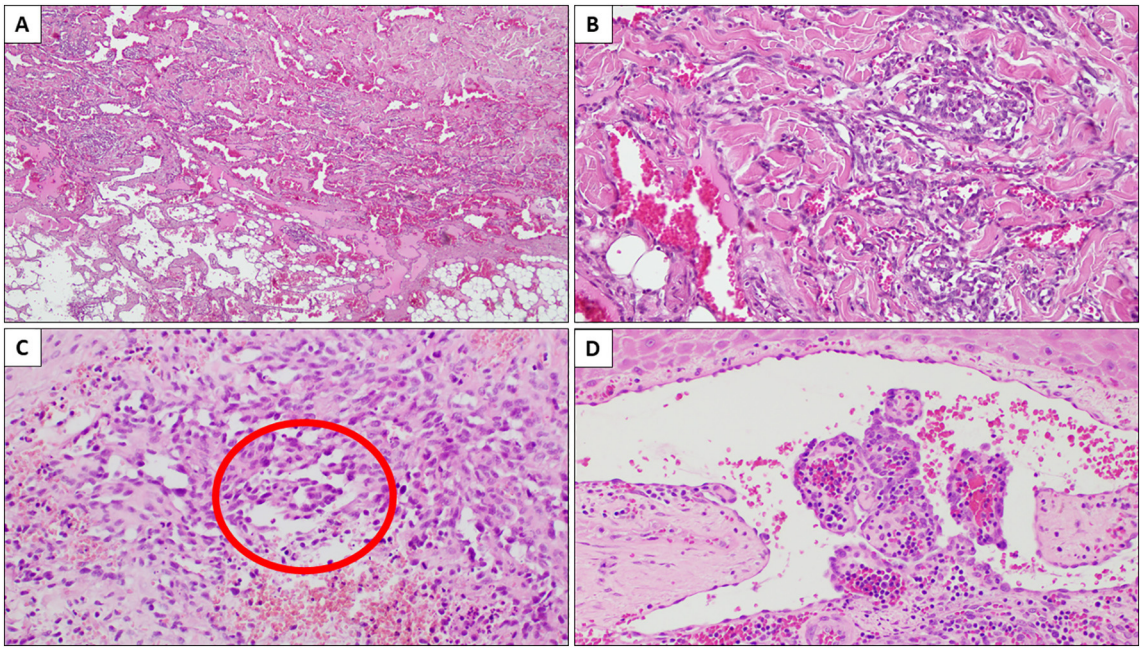

Fig. 5. Morphological findings of well-differentiated cAS. A) The neoplasm is constituted by obvious irregular vascular elements with erytrocytes-filled open lumina (H&E, original magnification x40). B) Vascular elements may show slit-like lumina and dissect the collagen bundles (H&E, original magnification 100×). C) The promontory sign (red circle), consisting in small vessel protruding into a larger vascular space, is typical of Kaposi's sarcoma, but may be present in well-differentiated cAS. Promontory sign is a histological hallmark of malignancy in well-differentiated vascular malignancies (H&E, original magnification 200×). D) Papillary projections into large vascular spaces may be present (H&E, original magnification 200×). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

diagnosis of cAS are summarized in Table 1. Generally, cASs are dermally-centred neoplasms with ill-defined and infiltrating borders, dissecting between the collagen bundles. Morphological details vary according to the degree of differentiation, and different patterns of growth and morphological findings may be present in the same neoplasm (Fig. 4). Histological hallmark of vascular differentiation is the

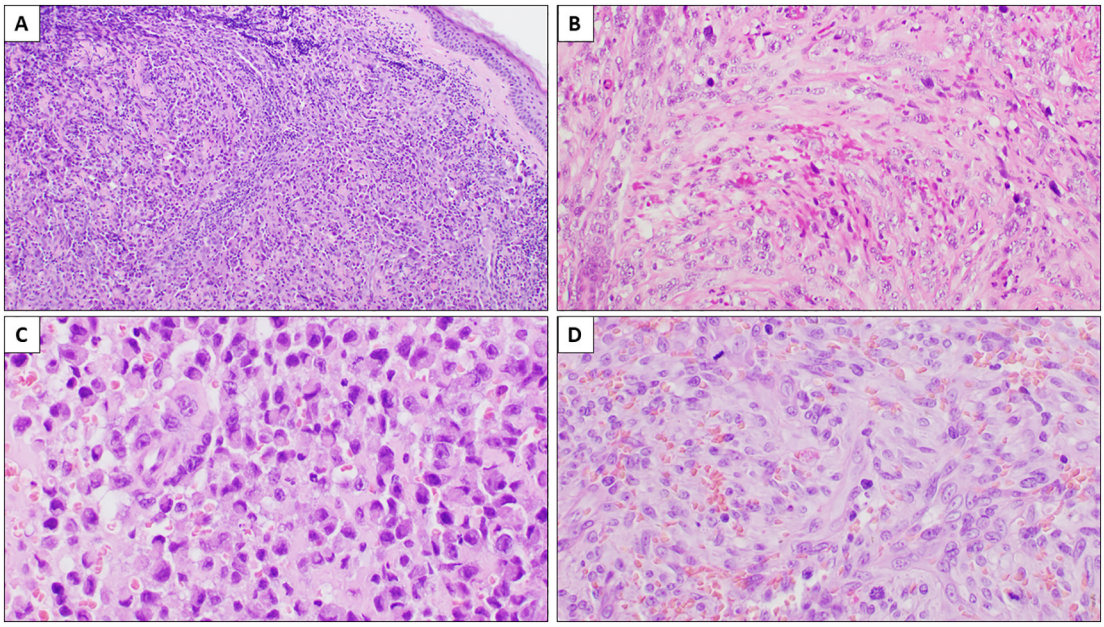

Fig. 6. Morphological findings of poorly-differentiated cASs. A) A dense lymphoid infiltrate may be present in some cASs, simulating a densely vascularized lymphoid neoplasm (H&E, original magnification 40×). B) The vascular differentiation may be subtle in poorly-differentiated cASs, consisting only in small intracellular lumina containing erythrocytes, or erythrocytes in single file (H&E, original magnification 200×). C) In epithelioid cAS, the neoplastic cells are large and polygonal, with abundant cytoplasm and atypical nuclei. In this example, the neoplastic cell are epithelioid with plasmacytoid features (H&E, original magnification 400×). D) In spindle cell cAS, the neoplastic cells are spindle-shaped, with poorly defined cellular borders, slightly eosinophylic cytoplasm and atypical nuclei. Some mitoses are evident (H&E, original magnification 400×).

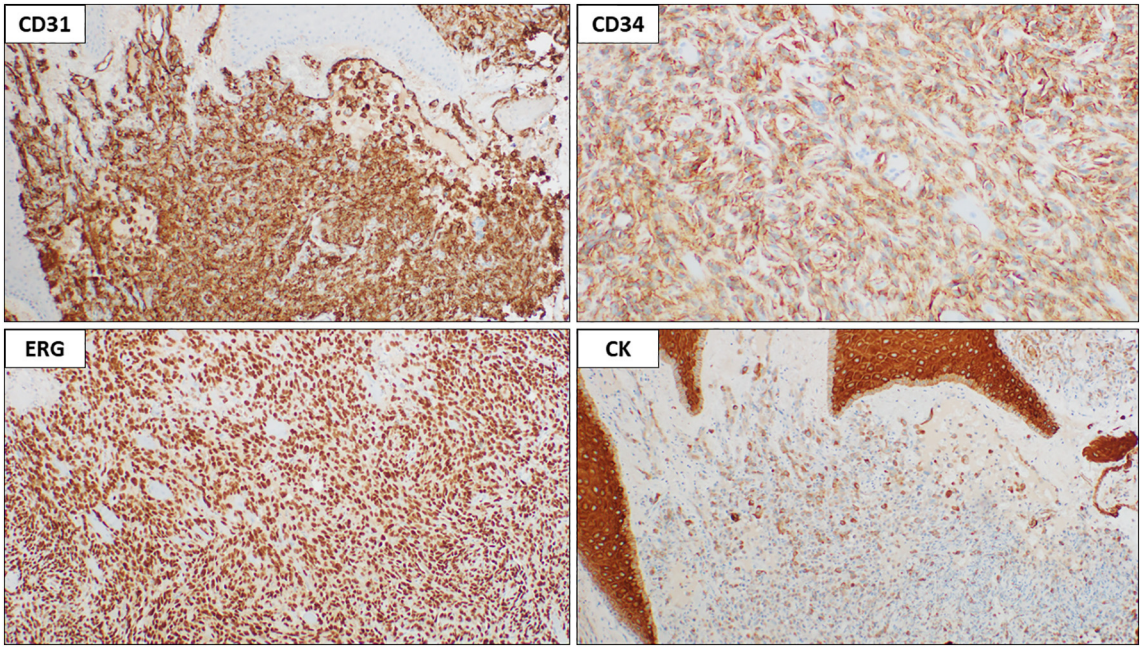

Fig. 7. Immunohistochemical findings. The most useful immunohistochemical markers of endothelial differentiation are CD31, CD34 and ERG. CD31 and CD34 are cytoplasmic markers, while ERG is a nuclear marker. Overall, CD31 and CD34 are sensitive but not highly specific markers, while ERG is actually the most sensitive and specific marker of endothelial differentiation. CD34 may be absent in head and neck cASs. Epithelioid cASs may express epithelial markers, such as cytokeratins. The expression is usually weaker if compared with the overlying epidermis. (Immunohistochemical stains, original magnification 100×).

presence of luminal spaces, often but not always filled with erythrocytes. Luminal spaces may consist of well-formed and opened lumina, or interconnecting irregular slot-like and poorly defined spaces. In the latter case, the accumulation of erythrocytes in single file within the slot-like spaces may be a clue [33]. The neoplasm may form papillae or solid nests within vascular lumina and the so called 'promontory-sign' may be observed, referring to small vessels surrounding and protruding into a larger, abnormal vascular space (Fig. 5). In poorly differentiated forms, the vascular differentiation may be very focal and subtle, consisting only in occasional intracellular lumina or intracellular erythrocytes (Fig. 6). Hemorrhages are often a prominent feature, with extravasated erythrocytes and hemosiderin accumulation. Sometimes, mainly in neoplasms with lymphatic differentiation, a variably dense lymphoid infiltrate is seen, which may even obscure the vascular

proliferation and simulate a lymphoma [34]. Although cASs usually show a diffuse growth pattern, other architectural patterns have been described, including nodular, micronodular and syncytial patterns [35]. Capillary lobules, which are characteristically seen in benign vascular neoplasms, may be present at the periphery of cASs, mainly in post-irradiation forms [36]. Cytological features of the neoplastic population in cASs are quite variable as well. In differentiated forms, endothelial cells are hobnail, with slightly atypical and hyperchromic nuclei; in poorly differentiated forms, neoplastic cells tend to be epithelioid or spindle-shaped, with pale eosinophilic cytoplasm and pleomorphic, vesicular and markedly atypical nuclei. Regardless of the degree of differentiation, the neoplastic population invariably shows mitotic activity and this is an important clue for malignancy, although not pathognomonic. Apart from epithelioid and spindle morphology, other rare cytological variants of cASs have been defined, including clear-cell, foamy-cell, signet-ring and granular-cell [35,37-40].

Immunohistochemistry plays a minor role in the diagnosis of cAS when morphological findings are clear-cut. However, in poorly differentiated forms immunohistochemistry is mandatory in order to demonstrate the presence of vascular differentiation. Few immunohistochemical studies on large series of cASs have been performed and available data is mainly inferred from studies comprising ASs from other sites. The most useful endothelial markers include CD31, CD34, FLI1 and ERG, which are consistently positive in ASs (Fig. 7). However, no antibody is entirely sensitive or specific, so the widest immunohistochemical panel should be used in suspected and poorly differentiated cases. Wang et al. investigated the sensitivity of these markers in a series of 24 hepatic ASs, and the sensitivity of CD34 and CD31 resulted in 87.5%, and 79%, respectively [41]. These results confirm those previously published by Miettinen et al. The Authors evaluated 27 ASs showing that CD31 was positive in 21/27 (77.8%) cases and CD34 in 25/27 (92.6%) [42]. Despite being relatively sensitive markers in ASs, CD31 and CD34 suffer from low specificity. In fact, CD34 expression is also seen in haematopoetic and fibrohistiocytic cells as well as in several non-vascular neoplasms (e.g. dermatofibrosarcoma protuberans, solitary fibrous tumour, epithelioid sarcoma and others) while CD31 may be positive in macrophages, histiocytes and plasma cells as well as other neoplasms (e.g. histiocytic sarcomas and occasional carcinomas, mesotheliomas, and undifferentiated pleomorphic sarcomas) [43,44]. Moreover, CD34 lose sensitivity in case of epithelioid cAS, according to the results from a study of Macchi et al. where CD34 resulted positive only in 10 out of 15 (66.7%) of cases [35]. ERG, an ETS family transcription factor, is considered the most sensitive and specific marker for endothelial differentiation. McKay et al. evaluated ERG expression in 23 head and neck cASs and it resulted positive in all cases. Furthermore, no ERG expression was observed in other non-vascular neoplasms included in the series (poorly differentiated squamous cell carcinomas, melanomas, atypical fibroxanthomas) [45]. FLI1, another ETS family transcription factor, seems to be almost equally sensitive but less specific than ERG, being expressed in several other neoplasms including leiomyosarcoma, squamous cell carcinoma, melanoma and atypical fibroxanthoma [45]. Some cASs may express lymphatic markers including D2-40, PROX-1 and VEGFR-3 [46,47]. Other less useful endothelial markers include von Willebrand factor, BNH9 and factor VIII-related antigen. Epithelioid cAS may express cytokeratins and epithelial membrane antigen (EMA), and this may represent a diagnostic pitfall with reference to the differential diagnosis with poorly differentiated carcinomas [48]. Currently, there is no established immunohistochemical marker allowing the distinction of cAS from benign vascular neoplasms. However, Myc expression is a novel candidate to play a role in this setting. In fact, as previously discussed, Myc expression is found in secondary cASs and in a subset of primary cASs [25]. Therefore, Myc immunohistochemical expression and gene amplification may help to differentiate cASs from non-malignant conditions that do not harbour *MYC* alterations, such as atypical vascular lesions, especially in case of cAS arising in radiation-exposed skin [24].

7. Prognosis

cASs are aggressive neoplasms with poor outcome and high rate of metastases, mainly to lungs, bones, liver and lymph-nodes [49]. The reported 5-year survival rates ranged from 10% to 40% in the largest published series [49,50]. Tumour histologic grade does not seem to be a good predictor of prognosis in cASs [51]. On the other hand, adverse prognostic factors in cAS include age $>$ 70 years, poor performance stadium, large tumour size ($>$ 5 cm), greater tumour depth, multifocality, presence of tumoral necrosis, presence of satellites at the time of diagnosis and epithelioid morphology [51,52]. Location significantly correlated with prognosis in a retrospective study by Lee et al. on 88 cutaneous and non-cutaneous ASs, with the scalp-located cases showing a worse prognosis [50]. Local recurrences are frequent and are at least partially determined by difficulties in achieving complete surgical excision, because of the ill-defined and infiltrative growth of the neoplasm. Indeed, resection margins resulted free in 76% to 82.1% of the cases in the largest series [50,53]. Regarding scalp-located cASs, local recurrences are even more common. In a series of 29 cASs of the scalp, resection with tumour-free margins was obtained in only 22.4% of cases [54]. Rouhani et al. and Dettenborn et al. demonstrated an improved survival in radically resected neoplasms [4,55]. New prognostic factors in cASs have been recently proposed in the literature. Among them, low immunohistochemical expression of CD99, a glycoprotein composing the neutral amino acid transporter (LAT1), seems to have an adverse prognostic role and correlate with the development of distant metastases [56]. In addition, thymidylate synthase, an enzyme catalyzing the methylation of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP), has been found to predict a worse progression-free survival in cASs patients of clinical stage 1 [57]. In contrast, high levels of tumour-infiltrating lymphocytes (TILs) seem to correlate with a more favourable prognosis in patients with AS [7,58]. In a study by Fuji et al., CD8-positive cytotoxic T lymphocytes correlated with longer metastasis-free interval, while CD4-positive T-cells and FOXP3-positive T-cells did not show significant association with prognosis [59]. These data may suggest that CD8-positive cytotoxic T lymphocytes have antitumour effects in cAS. Shimizu et al. evaluated the expression of PD1 and PD-L1 in a series of 52 cASs and found that PD-L1 was an independent prognostic factor in predicting worse outcome in cAS [60]. Moreover, Honda et al. reported a significant correlation between a high infiltration of PD-1-positive cells and favourable survival in stage 1 patients affected by cASs [61]. However, despite its correlation with a worse prognosis, PD-L1 is expressed in a remarkable proportion of cASs and may represent the rationale for testing immunotherapy in cAS patients [60]. Some cases of cASs treated with anti-PD-L1 immunotherapy achieving good results have already been reported [62,63].

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