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Abstract

Background

Cutaneous angiosarcoma (CAS) is a rare, extremely malignant vascular tumor. The optimum treatment for patients with CAS has not been defined because of its exremely rarity. As prognostic factors in patients with CAS, tumor less than 5 cm in size has a better prognosis. Although tumor differentiation in other sarcoma is an important prognostic factor, tumor differentiation in CAS is not a prognostic factor. CAS is thought as a collection of hemangiosarcoma, lymphangiosarcoma, tumors which cannot be classified as of vascular and lymphatic origin, or mixed tumor of both. Histogenesis of CAS have not been clarified yet. We tried to classify histogenesis by immunohistochemistry and evaluate the prognosis among histogeneses.

Methods

Using immunohistochemistry, we classified histogenesis of CAS in 20 patients who visited Osaka City University Hospital between 1998 and 2008.

Results

From the results of immunohistochemical staining with CD34 and D2-40, histogenesis of CAS can be divided into vascular type (CD34 positive D2-40 negative), mixed type (CD34 positive D2-40 positive), and lymphatic type (CD34 negative D2-40 positive). Vascular type was found in 2 cases, mixed type in 5 cases, and lymphatic type in 13 cases. Survival rates were not significantly affected by histogenesis, however, survival rate of mixed type was better than those of others.

Conclusions

CAS can be divided into vascular type, mixed type, and lymphatic type based on immunohistochemistry. Because of a small group, we did not suggest that histogenesis of CAS was related with prognosis. We speculate that antiangiogenic agents might be important in the treatment based on histogeneses in CAS. In the future, further accumulation of chemotherapeutic cases might upgrade histogenesis classification as an important prognostic

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factor in the treatment of CAS.

Key Words: Histogenesis; Immunohistochemistry; D2-40; Paclitaxel; Vascular endothelial growth factor

Introduction

Cutaneous angiosarcoma (CAS) is a relatively rare, extremely malignant mesenchymal tumor that occurs on the scalp and face in the elderly with a predilection in men[1]. Clinically, CAS usually arises innocuously as erythematous or bruise-like lesions on the scalp or face. The differentiation of angiosarcoma is classified into well-differentiated angiosarcoma (WDA), less well-differentiated angiosarcoma (LDA) and poorly differentiated angiosarcoma (PDA)[1]. Angiosarcoma is an extremely rare tumor comprising less than 1% of soft tissue sarcomas, which in turn account for 1% of adult solid malignancies[2]. In Japan, a nationwide survey of malignant skin tumor by the Japanese Skin Cancer Society reported about 40 angiosarcomas per year[3]. In a questionnaire on angiosarcoma by the Japanese Association of Dermatologic Surgery, 443 angiosarcoma patients were registered for ten years and angiosarcoma of the head and face accounted for 406 patients (90%)[4]. Little is known about the features, natural history, or optimal treatment of CAS. Management for CAS has been surgery, radiation therapy, and chemotherapy, and effective treatment for CAS has not been defined yet. Results with these treatments have been disappointing[5,6]. As the cause with it, the rarity of the disease can be thought. And another cause might be that the histogenesis of CAS has not been clarified, which is thought not to be a single disease but rather a collection of different malignancies, such as hemangiosarcoma, lymphangiosarcoma, undifferentiated from the vascular origin or lymphatic origin, and mixed tumor of both[7]. Recently, the monoclonal antibody D2-40 (antigen: podoplanin), a specific marker of lymphatic endothelia, has been found[8]. Immunohistochemically, D2-40 enabled us to study the precise origins of CAS. It is reported that angiosarcoma is derived from both vascular endothelial cells and lymphatic endothelial cells, or lymphatic endothelial cells[8-10].

In this study, we evaluated that CAS clinical course, symptom, and prognosis against 20 cases experienced for 11 years in Osaka City University Hospital (OCUH). Next, we examined the expression of a selective lymphatic marker, D2-40, and compared its reactivity with the expression of vascular endothelial markers, such as von Willebrand Factor (vWF), and CD34 and CD31 against CAS. From the results of immunohistochemistry, we tried to classify the histogenesis of angiosarcoma. We also examined the prognosis among histogeneses. Finally we speculated the possibility of usage of anti-angiogenic and anti-lymphangenic agents for CAS.

Methods

Clinical Database

We examined 20 patients with CAS who visited OCUH between 1998 and 2008. Clinical information was obtained by a retrospective review of the patient's records. The records were examined for the following data: age at presentation, gender, race, clinical site of tumor presentation, type of disease, delay of diagnosis, period of follow-up, time to recurrence, time to metastases, disease-free survival, and overall survival. The period of follow-up, time to

recurrence, time to metastases, disease-free survival, and overall survival were evaluated in 18 patients, excluding 2 cases not treated at OCUH. Age was at presentation, time to local recurrence and metastasis was calculated as the time from presentation at OCUH to the time of first local recurrence and metastasis. Local recurrence was defined as clinically or radiologically documented tumor regrowth at the primary site; distant metastases were defined as clinically or radiologically documented tumor regrowth at sites distant from the primary site.

Tissue preparation

Biopsy specimens were taken at the first examination, or tissue was obtained at initial surgery. Specimens were fixed in formalin, embedded in paraffin, and used in this study. Sections were cut at 4 micro-meter thickness.

Evaluation of differentiation

Hematoxylin and eosin (H&E) stains were performed for all cases. CAS was differentiated using H&E at high magnification (×210) based on morphological criteria. Cases of CAS were classified into well-differentiated angiosarcoma, less well-differentiated angiosarcoma, and poorly differentiated angiosarcoma. Various tumor differentiations were sometimes seen within the same tumor, in which case the predominant pattern was adopted for classification purposes. WDA (Fig. 1A) was diagnosed when the tumor exhibited irregular vascular channels lined by a single layer of somewhat enlarged endothelial cells, the nuclei of which protruded into the vascular lumen, and irregular vascular channels infiltrated between collagen bundles. LDA (Fig. 1B) was diagnosed when the tumor showed enlarged endothelial cells and pronounced nuclear atypia, with intraluminal papillary projections. PDA (Fig. 1C) was diagnosed when the tumor had indistinct vascular spaces and large polymorphic cells.

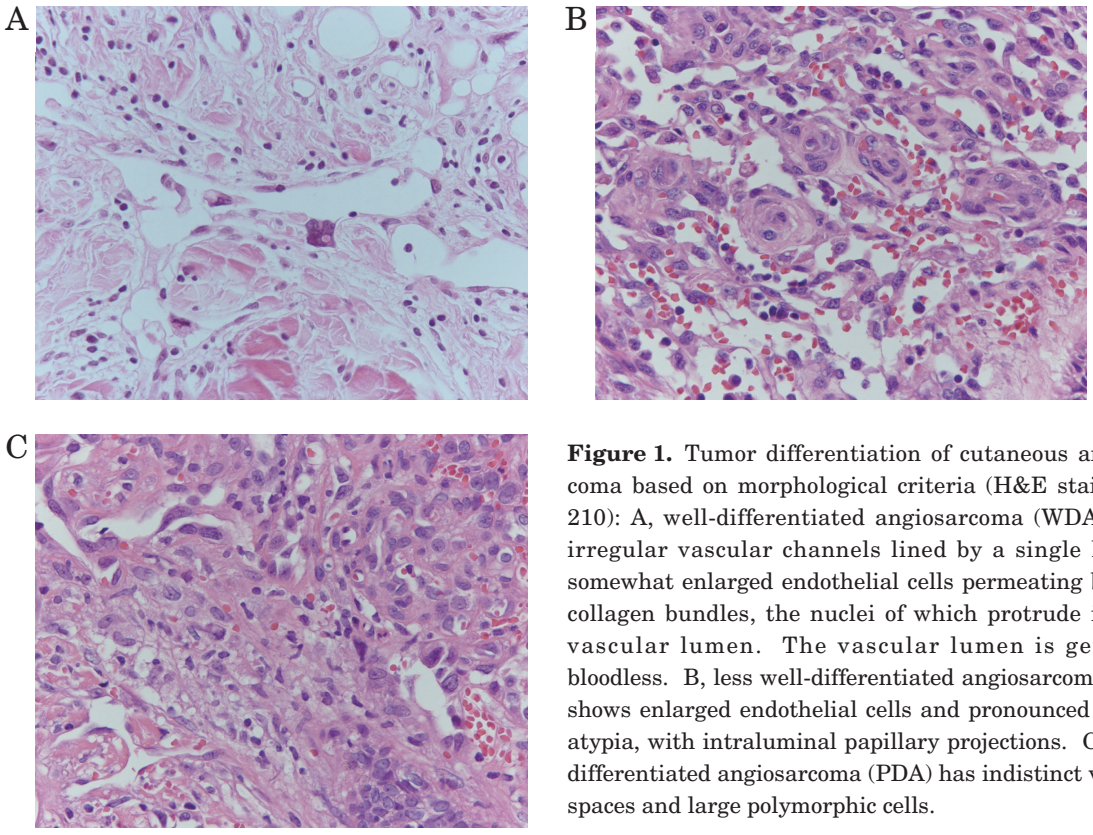

Figure 1. Tumor differentiation of cutaneous angiosarcoma based on morphological criteria (H&E staining, × 210): A, well-differentiated angiosarcoma (WDA) forms irregular vascular channels lined by a single layer of somewhat enlarged endothelial cells permeating between collagen bundles, the nuclei of which protrude into the vascular lumen. The vascular lumen is generally bloodless. B, less well-differentiated angiosarcoma (LDA) shows enlarged endothelial cells and pronounced nuclear atypia, with intraluminal papillary projections. C, poorly differentiated angiosarcoma (PDA) has indistinct vascular spaces and large polymorphic cells.

Immunohistochemistry

Immunohistochemical staining was performed using anti-vWF (Dako, Denmark) antibody at 1:250 dilution, anti-CD31, endothelial cell (clone JC 70A) (Dako, Denmark) antibody at a 1:50 dilution, diluted anti-CD34 (clone QBEnd/10) (Dako, Denmark) antibody, or diluted D2-40 (Nichirei, Japan) antibody, employing a DAKO LSAB2 kit/HRP (Dako, USA) and the DAB Liquid System (Dako, Japan). Both negative and positive controls were used in all cases, with Negative control Mouse IgG1 (Dako, Japan) and benign hemangioma and lymphangioma tissue as positive controls. CD34 is expressed on immature hematopoietic stem/progenitor cells and capillary endothelial cells. vWF antigen is present in plasma, in the Weibel-Pallade bodies of endothelial cells, in platelets, as well as in the subendothelial matrix of the vessel wall. CD31 is expressed on all continuous endothelia, including those of arteries, arterioles, venules, veins, and non-sinusoidal capillaries. D2-40 (antigen: podoplanin), selective lymphatic endothelial marker is a monoclonal antibody to an MW 40000 O-linked sialoglycoprotein that reacts with a fixation-resistant epitope on lymphatic endothelium[8]. Sections of paraffin-embedded tissues were dewaxed through graded concentrations of ethanol. For immunostaining, heat-inducted epitope retrieval by citric buffer at 95℃ for 45 min was performed for all specimens. The sections were first incubated in methanol containing 0.3% H_2O_2 to inactivate endogenous peroxidase. The sections were then incubated with the primary antibody overnight at 4℃. The subsequent development of antibody-bridge labeling was induced by the streptavidin-biotin-peroxidase method using Dako LSAB2 kit/HRP. The sections were then reacted in a DAB Liquid System, counterstained with 5% methyl green, and mounted. The distribution of positive staining was scored, with 0 indicating negative, 1+ indicating <10% staining, 2+ indicating 10-50% staining, and 3+ indicating >50% staining.

Statistical Analysis

Patient information and clinical characteristics were summarized using medians. Survival was estimated using the Kaplan-Meier method with 95% confidence intervals, with disease-specific mortality, local recurrence, and distant metastasis as endpoints. The time to occurrence of any event was calculated from the date of presentation at OCUH to the date when the event was recorded, or the event was censored at the date of last follow-up assessment (08/01/2010) in event-free patients. Patient survival data were compared using the log-rank test.

Results

Clinical database

Clinical characteristics are summarized in Table 1. The 20 patients were 11 men and 9 women (male:female, 1.2:1.0). The median age at presentation was 72.5 (range, 52-88) years. All patients were Japanese. The median time to diagnosis was 3.5 months, with a range from 1 to 27 months. Sites of disease were 17 (85%) on the scalp, 2 (10%) on the scalp and face, and 1 (5%) on the face. Types of disease were 11 (55%) plaque, 6 (30%) plaque and nodules, and 3 (15%) nodules.

Differentiation

In the differentiation of CAS, there was 1 case of WDA, 7 cases of LDA, and 12 cases of PDA, respectively (Table 2).

Table 1. Patient Characteristics

Characteristic	No. (%)
Age (yrs)	
Median	72.5
Range	52-88
Gender	
Female	9 (45)
Male	11 (55)
Delay in diagnosis (mos)	
Median	3.5
Range	1-27
Site	
Scalp	17 (85)
Scalp/Face	2 (10)
Face	1 (5)
Type of disease	
Plaque	11 (55)
Plaque/Nodule	6 (30)
Nodule	3 (15)

n=20 patients

Table 2. Profile of cutaneous angiosarcoma patients, differentiation, immunohistochemical staining results and histogenesis

No	Sex/Age in years	Site	Type of the disease	Differentiation	CD34	vWF	CD31	D2-40	Histogenesis
1	F/69	Scalp/Face	Plaque	WD	3+	1+	2+	3+	M
2	F/85	Scalp	Nodule	LD	3+	0	0	0	V
3	M/66	Scalp	Plaque	LD	3+	3+	2+	0	V
4	M/52	Scalp	Plaque/Nodule	LD	3+	3+	3+	3+	M
5	M/73	Scalp	Plaque/Nodule	LD	3+	2+	3+	3+	M
6	F/77	Scalp	Plaque/Ulcerations	LD	0	0	3+	3+	L
7	M/86	Scalp	Plaque/Ulcerations	LD	0	0	2+	3+	L
8	M/61	Scalp	Plaque/Ulcerations	LD	0	0	0	3+	L
9	F/88	Scalp	Plaque/Nodule	PD	3+	2+	3+	3+	M
10	M/64	Face	Plaque	PD	2+	2+	3+	3+	M
11	M/74	Scalp	Plaque/Nodule	PD	0	0	0	3+	L
12	F/76	Scalp	Plaque	PD	0	0	2+	3+	L
13	F/62	Scalp/Face	Plaque/Ulcerations	PD	0	3+	3+	3+	L
14	F/76	Scalp	Plaque	PD	0	3+	3+	3+	L
15	M/74	Scalp	Plaque/Nodule	PD	0	0	0	3+	L
16*	M/66	Scalp	Plaque	PD	0	0	1+	3+	L
17	F/87	Scalp	Nodule	PD	0	1+	2+	3+	L
18	M/66	Scalp	Plqaue/Nodule	PD	0	0	2+	3+	L
19*	F/72	Scalp	Plaque	PD	0	0	2+	3+	L
20	M/65	Scalp	Nodule	PD	0	0	2+	2+	L

WD, well-differentiated angiosarcoma; LD, less well-differentiated angiosarcoma; and PD, poorly differentiatied angiosarcoma. V, vascular type, M, mixed type, and L, lymphatic type. No.16* and No.19* were excluded in suvival analysis for untreated.

Immunohistochemical findings

Immunohistochemical results are summarized in Table 2. In 20 cases of CAS, immunohistochemistry demonstrated CD34 in 7 cases, vWF in 9 cases, CD31 in 16 cases, and

D2-40 in 18 cases. CD34 expression was predominantly on the membranes of tumor cells (Fig. 2A). Thus, the luminal surfaces were particularly well delineated by this marker. vWF expression showed patchy, weak, diffuse staining on sections (Fig. 2B). CD31 expression was granular and cytoplasmic in tumor cells (Fig. 2C). D2-40 expression showed diffuse staining of tumor cells (Fig. 2D).

Histogenesis

From the results of immunohistochemical staining with CD34 and D2-40, the histogenesis of angiosarcoma was divided into three staining types: vascular type (CD34 positive D2-40 negative) (Fig. 3), mixed type (CD34 positive D2-40 positive) (Fig. 4), and lymphatic type (CD34 negative D2-40 positive) (Fig. 5). There were 2 cases of vascular type, 5 cases of mixed type, and 13 cases of lymphatic type (Table 2).

Differentiation and histogenesis

We evaluated the association of histogenesis with differentiation. WDA (1 case) was mixed type in 1 case, LDA (7 cases) was vascular type in 2 cases, mixed type in 2 cases and lymphatic type in 3 cases. Poorly differentiated angiosarcomas (12 cases) were mixed type in 2 cases and lymphatic type in 10 cases. Only 2 cases of LDA were the vascular type. Differentiation was not correlated to histogenesis (Table 3).

Angiosarcoma-specific survival, recurrence and metastasis

Two patients were excluded for untreated in OCUH. At a median follow-up of 19 (range, 3-48) months (n=18), the tumor recurred in 12 (67%) of 18 patients. Local failure was defined as

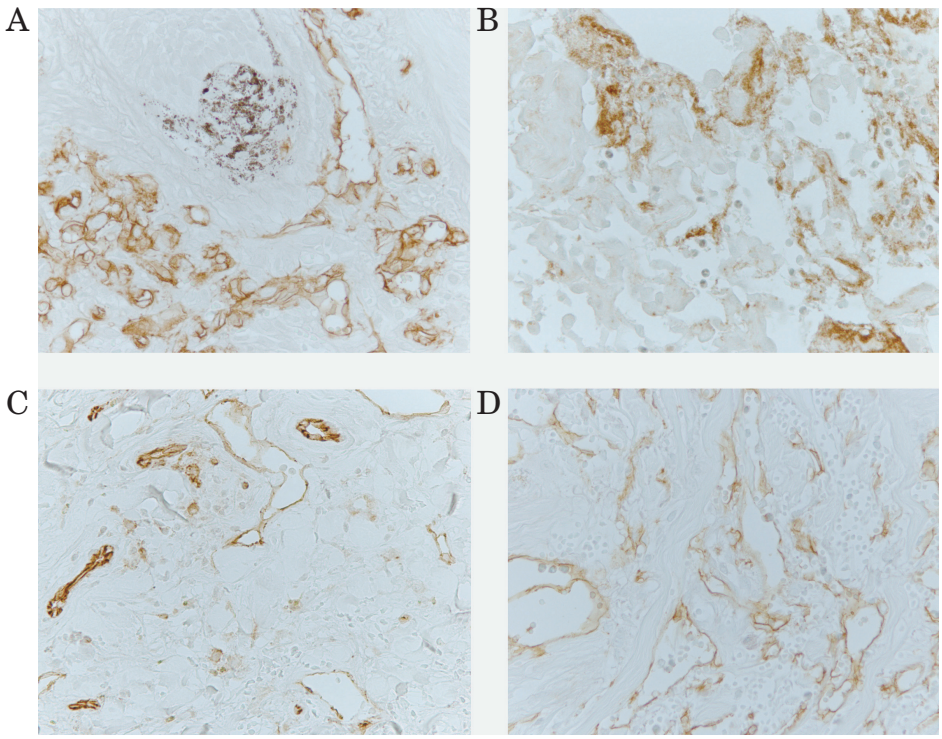

Figure 2. A, CD34 antibody staining showed positive cells composing of vascular structure in the tumor tissue. B, von Willebrand Factor antibody staining showed patchy, diffuse staining at the lumen of vascular structure. C, CD31 antibody staining showed granular staining of the endothelial cells both in vascular and lymphatic strucutre. D, D2-40 staining showed diffuse staining of the lymphatic endothelial cells.

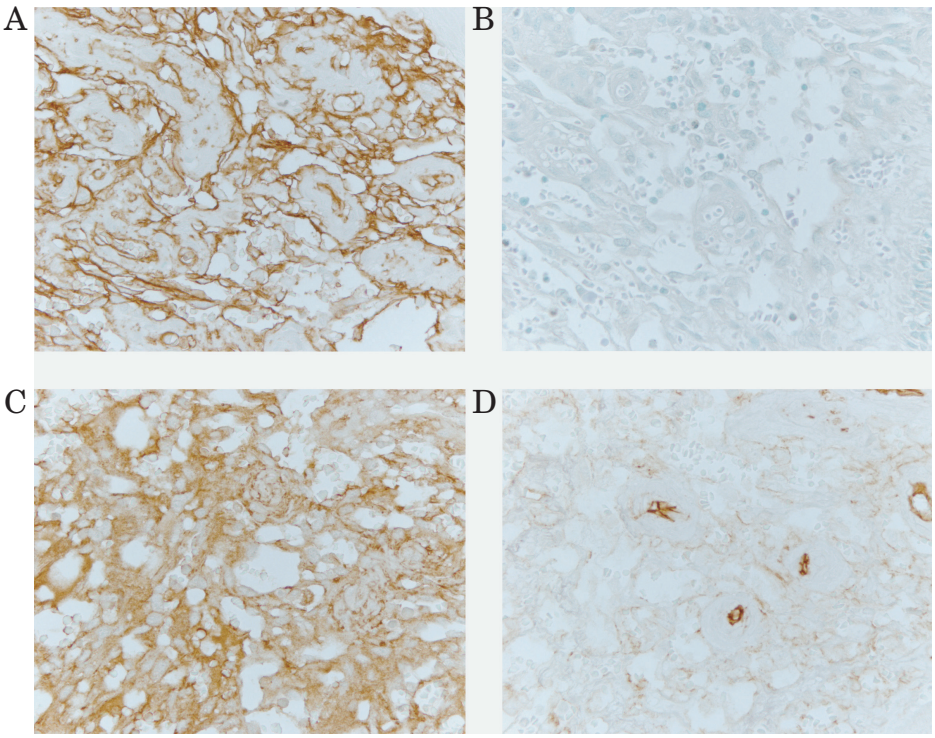

Figure 3. Immunohistochmeical finding of CD34, D2-40, von Willebrand Factor (vWF), and CD31 were showed (Table 2, No.3). A, CD34 and C, vWF were expressed in irregular vascular channels. B, D2-40 was negative in irregular vascular channels. D, CD31 was almost negative in irregular vascular channels. Vascular type (CD34 positive D2-40 negative) suggested that cutaneous angiosarcoma could originate from vascular endothelia.

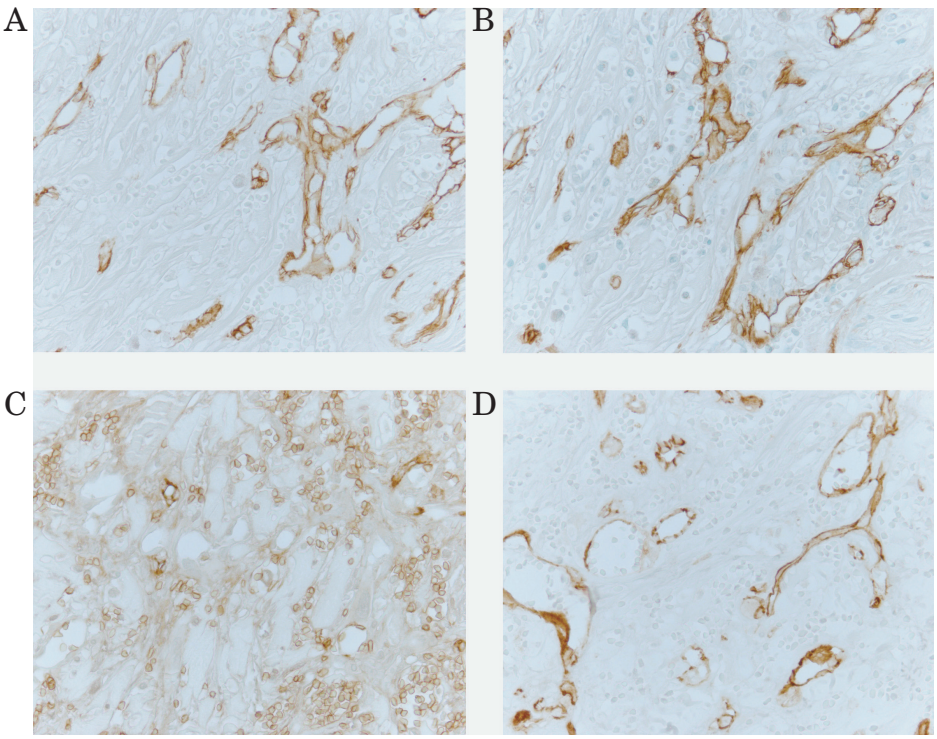

Figure 4. Immunohistochmeical finding of CD34, D2-40, von Willebrand Factor (vWF), and CD31 were showed (Table 2, No.9). A, CD34, B, D2-40, and D, CD31 were expressed at the endothelial cells of irregular channels. C, vWF was positive at the lumen and blood cells. Mixed type (CD34 positive D2-40 positive) suggested that cutaneous angiosarcoma could originate both from vascular and lymphatic endothelia.

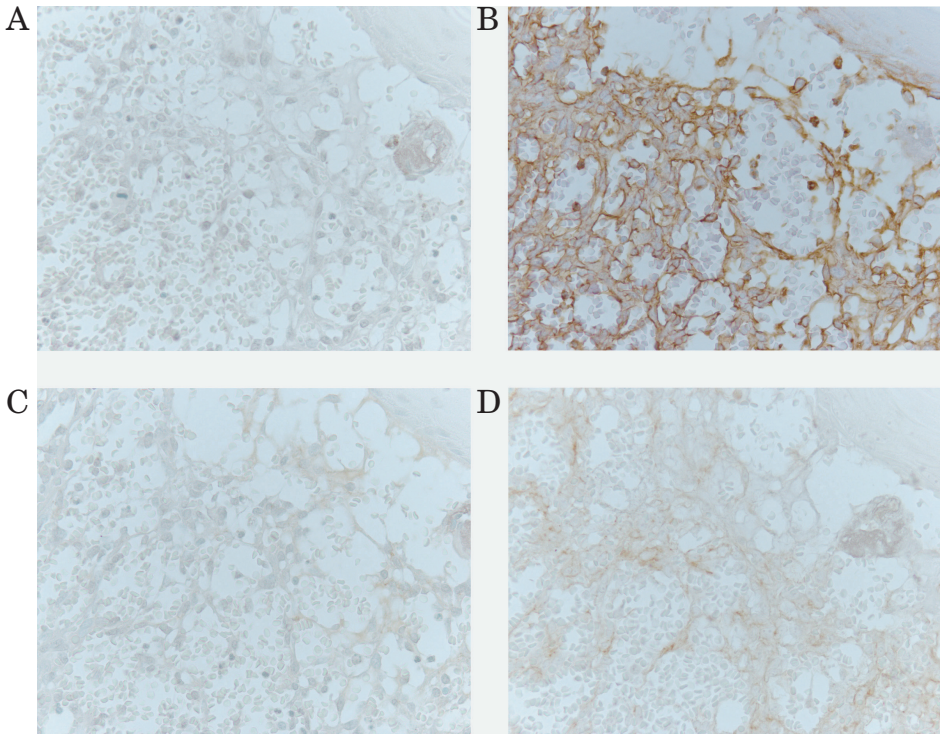

Figure 5. Immunohistochmeical finding of CD34, D2-40, von Willebrand Factor (vWF), and CD31 were showed in cutaneous angiosarcoma (Table 2, No.8). A, CD34, C, vWF, and D, CD31 were negative in irregular channels. B, Only D2-40 was positive in the tumor cells. Lymphatic type (CD34 negative D2-40 positive) suggested that cutaneous angiosarcoma could originate from lymphatic endothelia.

Table 3. Correlation between differentiation and histogenesis of cutaneous angiosarcoma

Differentiation (No.)	Histogenetic type		
(n=20)	Vascular	Mixed	Lymphatic
WDA (1)	0	1	0
LDA (7)	2	2	3
PDA (12)	0	2	10

WDA, well-differentiated angiosarcoma; LDA, less well-differentiated angiosarcoma; and PDA, poorly differentiated angiosarcoma.

recurrence at the primary site with or without distant disease. Four patients had metastases at presentation. Sites of metastasis included the lymph nodes in 3 patients and the liver and spleen in 1 patient. Median survival of 4 patients with metastasis was 10 (range, 3-26) months. Local recurrence developed in 7 patients (39%) and distant metastasis in 12 patients (67%). Time to local recurrence was a median of 10 (range, 5-18) months and time to metastasis was a median of 14.5 (range, 2-43) months (Table 4).

Our treatments were surgery in 7 cases, radiation therapy in 15 cases, interleukin-2 administration in 5 cases and chemotherapy (docetaxel hydrate) in 7 cases. With regard to survival, at last follow-up, 10 patients (56%) had died of the disease, 3 patients (17%) had died of other causes, 3 patients (17%) were lost to follow-up, and 2 patients (10%) were alive. The 4-year disease-free survival rate was 6.7% (Fig. 6A) and the 4-year overall survival rate was 12.5% (Fig.

6B).

Survival rate by differentiation and histogenesis

Survival rate by the differentiation of angiosarcoma was not a significant risk for WDA (n=1),

Table 4. Time to recurrence or metastasis, and survival with cutaneous angiosarcoma

Variable	period (mos)
Follow-up (n=18)	
Median	19
Range	3-48
Time to recurrence (n=7)	
Median	10
Range	5-18
Time to metastasis (n=12)	
Median	12
Range	2-43
Disease-free survival (n=18)	
Median	10
Range	0-48
Overall survival (n=18)	
Median	19
Range	3-48

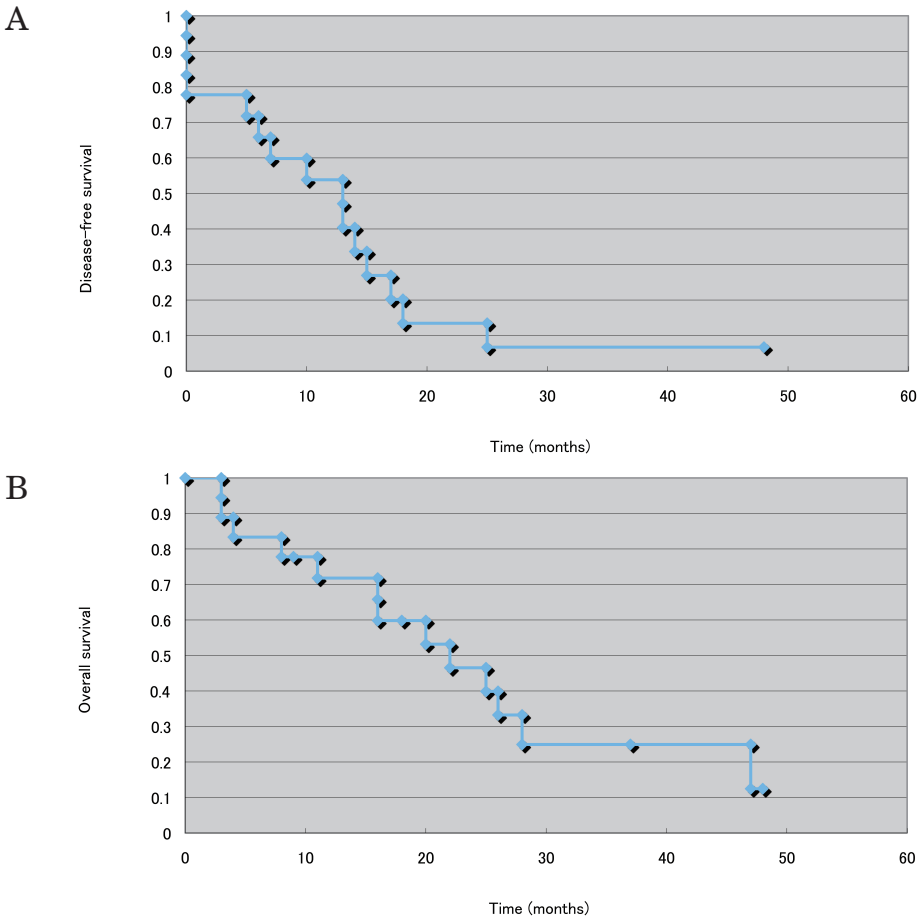

Figure 6. A, Disease-free survival rate. B, Overall survival rate.

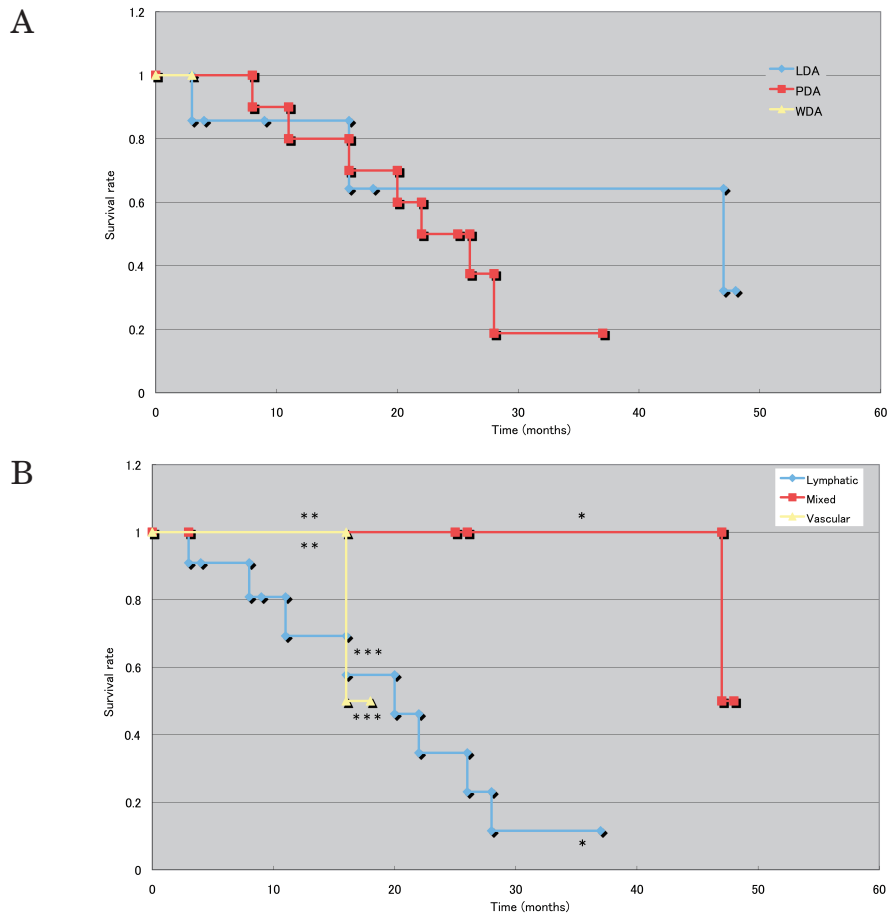

Figure 7. A, Kaplan-Meier curves according to differentiation of cutaneous angiosarcoma. WDA, well-differentiated angiosarcoma; LDA, less well-differentiated angiosarcoma; and PDA, poorly differentiated angiosarcoma. B, Kaplan-Meier curves according to histogenesis types. V, vascular type; M, mixed type; and L, lymphatic type. There was no difference among 3 types (p=0.086). *, There was significant difference between lymphatic type and mixed type (p=0.0261). **, There was no difference between vascular type and mixed type (p=0.206). ***, There was no difference between lymphatic type and vascular type (p=0.952).

LDA (n=7), and PDA (n=10), p=0.78 (Fig. 7A). Survival rate by the histogenesis of angiosarcoma was not a significant risk for vascular type (n=2), mixed type (n=5), and lymphatic type (n=11), p=0.09 (Fig. 7B). The survival rate of mixed type was better than that of others.

Discussion

CAS is an extremely progressive malignant mesenchymal tumor that frequently occurs on the face and scalp in the elderly[1]. The optimal treatment for CAS has not been defined because of its extreme rarity[2]. CAS is classified into (a) angiosarcoma of the face and scalp in the elderly; (b) angiosarcoma (lymphangiosarcoma) secondary to chronic lymphedema; and (c) angiosarcoma as a complication of chronic radiodermatitis or arising from the effects of severe skin trauma or ulceration[1]. CAS usually occurs on the face and scalp in elderly men with an estimated male-to-female ratio of 3:1 and an average age at presentation of 63 years[2,11]. CAS mainly affect Caucasians, sometimes Asians, but rarely blacks[1]. Clinically, the appearance of CAS is quite variable. Most early lesions begin as ill-defined, bruise-like areas with an indurated border. The

lesion may often be multifocal. Lesions show purpura, erythema, plaques with flat infiltrating areas or nodules, and they occasionally bleed or ulcerate[1]. Metastasis to nodes or internal organs usually arises as a late complication, with many patients dying as a result of extensive local disease. CAS commonly metastasizes to the lungs, as do other soft tissue sarcoma. The overall prognosis for patients with CAS is very poor[1]. In our series, the type of disease was 11 (55%) plaque type with purpura, erythema, and induration, 6 (30%) plaque/nodular type, and 3 (15%) nodular type. The location of angiosarcoma was 17 (85%) on the scalp, 2 (10%) on the scalp and face, and 1 (5%) on the face. Of 18 patients treated at OCUH, 16 patients had metastases. 9 metastases occurred in the lymph nodes, 6 in the lung, 2 in the liver, and 1 each in the digestive tract, spleen, and bone marrow, respectively. In 4 autopsy cases, 3 metastases were in the lymph nodes, 3 in the lung, and 1 each in the liver, spleen and digestive tract, respectively. The median survival time was 19 (range, 3-48) months (n=18) and the 4-year survival rate was 12.5%. Our experience was similar to the nationwide survey of malignant skin tumor by the Japanese Skin Cancer Society, which showed an average survival time was 19.52 months and 5-year survival rate of 9%; the 5-year survival rate was 12-33% in the English literatures[1,12-14]. As prognostic factors in patients with CAS, tumor size is important, and patients with tumors <5 cm in greatest dimension had a significantly better prognosis than patients with larger lesions[5,12]. Although tumor grade is an important prognostic factor in patients with other types of sarcoma, some reported that prognosis is independent of grade in patients with angiosarcoma[5,12,15]. In our series, also, there was no difference among differentiation (WDA: 1 case, LDA: 7 cases, PDA: 10 cases) in survival rate, p=0.78.

What histogenesis of CAS is not classified might cause unclear evaluation of the prognosis for CAS. With regard to histogenesis, it has not been defined yet. In fact, there is some evidence to suggest that CAS could be not of vascular but of lymphatic endothelial cell origin[1]. For example, the vascular lumen in well-differentiated lesions of CAS is generally bloodless. On electron microscopic examination, the ovoid laminated organelle-like Weibel-Palade bodies characteristic of vascular endothelial cells are absent in most CAS. CAS is thought to be not a single disease but rather a collection of hemangiosarcoma, lymphangiosarcoma, tumors which cannot be classified as of vascular and lymphatic origin, or mixed tumor of both[7,16]. However, it has not precisely proved histogenesis of CAS yet. In immunohistochemical studies, conventional antibodies specific for vascular endothelia: antibodies to CD34, vWF, and CD31 were used. CD34 is expressed on immature hematopoietic stem/progenitor cells and capillary endothelial cells. vWF antigen is present in plasma, in the Weibel-Pallade bodies of endothelial cells, in platelets, as well as in the subendothelial matrix of the vessel wall. CD31 is expressed on all continuous endothelia, including those of arteries, arterioles, venules, veins, and non-sinusoidal capillaries. In the study used these antibodies specific for vascular endothelia, Orchard GE et al reported that most CAS tumors were CD31 positive, UEA-1 positive, CD34 negative, and vWF negative, an immunohistochemical profile which was consistent with the lymphatic derivation; however, because CD31 is a pan-endothelial cell marker, the precise distinction between vascular and lymphatic endothelia was impossible[17]. Recently, the selective lymphatic endothelial marker D2-40 (antigen: podoplanin) was reported. D2-40 is a monoclonal antibody to an MW 40000 O-linked sialoglycoprotein that reacts with a fixation-resistant epitope on lymphatic endothelium. In normal tissues, D2-40 stained the endothelium of lymphatic channels

but not of blood vessels, including arteries and capillaries[8]. Breiteneder-Geleff S et al reported that because 10 of 11 angiosarcomas coexpressed podoplanin and endothelial markers of blood vessels, they concluded that G3 angiosarcoma (poorly differentiated angiosarcoma) showed the mixed expression of both lymphatic and blood vascular endothelial phenotypes[10]. Kahn HJ et al reported that, based on their immunoreactivity with D2-40 and CD31 staining, angiosarcomas can be divided into subsets that originate from one of two distinct progenitor cell types, one restricted to differentiating along the blood vessel endothelial lineage and the other capable of differentiating along both the lymphatic and blood vessel lineages[8]. Fukunaga M et al reported that 4 of 7 cases of angiosarcoma were strongly positive for D2-40. These findings suggest partial lymphatic endothelial differentiation. Subsets of angiosarcomas show both vascular and lymphatic endothelial differentiation[9].

These reports were composed from a small group, which was less than 20 cases and was not limited to CAS in the scalp and face. There have not been any previous reports about prognosis based on histogeneses for CAS. In this study, we tried to classify based on histogenesis of CAS in the scalp and face. Because CD34 is not expressed in the lymphatic endothelia but in the vascular endothelia, and CD31 is a pan-endothelia marker, which is co-expressed in both vascular and lymphatic endothelia, and D2-40 is a selective lymphatic marker, CAS could be divided into three types based on immunochemistry: vascular type (CD34 positive D2-40 negative), mixed type (CD34 positive D2-40 positive), and lymphatic type (CD34 negative D2-40 positive), with 2 cases of vascular type, 5 of mixed type, and 13 of lymphatic type. And we tried to examine the prognosis among histogeneses. There was no difference among the histogeneses in the survival rate ($p=0.09$), however, survival rate of mixed type was better than those of others.

In molecular biologic study about signal transduction in angiogenic and lymphangiogenic, also, there was a report about vascular endothelial growth factor receptor (VEGFR)-2 expression[18]. The majority of CAS express vascular endothelial growth factor (VEGF)-A and C, potent angiogenic and lymphangiogenic factors that may enhance CAS proliferation, survival, migration, and invasion via the activation of VEGFRs[19]. VEGF-A plays an important role in angiogenesis and vascular permeability. VEGF-A induces angiogenesis acting through VEGFR-1 and VEGFR-2. Similarly, angiogenesis and vascular permeability play a central role in development of angiosarcoma. VEGF-C and VEGF-D induce lymphangiogenesis through VEGFR-2 and VEGFR-3[19]. VEGFR-2 plays an important role in the development of angiosarcomas. Low or a lack of VEGFR-2 expression was associated with an unfavorable prognosis[18]. VEGFR-2 expression in CAS might be related with the histogenesis of CAS.

In the treatment for CAS in the scalp and face, surgery, radiation, recombinant interleukin-2 administration, and chemotherapy have been used[4,12]. Results with surgery alone have been disappointing, with high rates of recurrence and an inability to obtain clear surgical margins[5,6]. Radiation therapy has been offered as possible adjuvant therapy[5,6,12]. Chemotherapeutic agents used to be doxorubicin and ifosfamide[19]. Recent reports suggest the potential efficacy of paclitaxel in the treatment of metastatic or locally advanced CAS, especially on a low-dose, weekly schedule[20,21]. Paclitaxel has antiangiogenic and apoptotic effects[22,23]. A response rate of 89% was seen in patients with angiosarcoma of the scalp or face[21]. In molecular target treatment, sorafenib, a multikinase inhibitor that acts by inhibiting tumor growth and

disrupting tumor microvasculature through antiproliferative, antiangiogenic, and proapoptotic effects[24], is potentially useful against CAS[25]. Lahat et al reported that cases to surgery were limited and treatment for CAS mainly performed chemo-radiation therapy rather than surgery and better prognosis[19]. We speculate that it is important to administer anticancer drug in the early period of treatment in order to prevent recurrence and metastasis. We should notice effect of anticancer drug, chemotherapeutic agents or molecular target treatment agents based on histogenesis and/or VEGF and VEGFR expression. As we had used docetaxel hydrate, a similar pharmacological agent to paclitaxel, only in 7 cases, we could not state the efficacy of antiangiogenetic or antilymphatic inhibition in our clinical cases. With regard to chemotherapy for CAS, we need further experiences.

In summary, CAS is one of the worst aggressive malignant angioneoplasms. The best goal of treatment associated with the survival prognosis is to prevent metastasis from the early period of treatment. The treatment with expected efficacy is anticancer therapy using paclitaxel and molecular-targeted treatment's agents. It is of note that these drugs target antiangiogenetic or antilymphatic inhibition. Meanwhile, the histogenesis of angiosarcoma has not yet been defined. It is considered that CAS is not a single disease but rather a collection of vascular or lymphatic tumor. In this study, the histogenesis of angiosarcoma was vascular endothelia type, mixed type of vascular endothelia and lymphatic endothelia, and lymphatic endothelia type. There was no significantly difference in the survival rate among histogeneses, however, survival rate of mixed type had better than those of others. In the future, further accumulation of chemotherapeutic cases might upgrade histogenesis classification as an important prognostic factor in the treatment of CAS.

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