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Intravascular ("intimal") epithelioid angiosarcoma: clinicopathological and immunohistochemical analysis of three cases

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Abstract Angiosarcomas are rare malignant mesenchymal tumours, characterized morphologically by anastomosing vascular channels lined by atypical and proliferative active endothelial cells. An epithelioid cytomorphology of tumour cells is often seen focally in angiosarcoma, whereas purely epithelioid angiosarcomas are rare. Although angiosarcomas show a vascular differentiation they are almost never confined to pre-existing blood vessels. We describe three cases of intravascular epithelioid angiosarcoma arising in the carotid artery of a 60-year-old man, in the infrarenal part of the abdominal aorta and both renal arteries of a 69-year-old woman, and in the abdominal aorta of a 68-year-old man. In all cases malignant tumour tissue was found incidentally after disobliteration of thrombosed vessels. Histologically, purely epithelioid angiosarcoma composed of solid sheets of epithelioid tumour cells was seen; immunohistochemistry confirmed the endothelial differentiation of neoplastic cells. The reported cases show that angiosarcoma can occasionally arise within a pre-existing vessel.

Key words Angiosarcoma · Epithelioid angiosarcoma · Intravascular angiosarcoma · "Intimal" sarcoma · Soft tissue tumours

Introduction

Angiosarcoma is a rare and clinically aggressive mesenchymal neoplasm occurring in different clinical settings. Cutaneous angiosarcomas arise mainly in the head and neck region of elderly patients, in patients with chronic lymphoedema of the limbs (so-called lymphoedematous angiosarcoma), or after radiotherapy. Furthermore, angiosarcomas occur in the skeletal system, in the breast, in parenchymatous organs (liver, spleen, ovary, thyroid gland), and in soft tissues [3]. Histologically, angiosarcoma is characterized by a diffuse rather than lobular or nodular growth pattern, as seen in benign vascular lesions. At higher power, the anastomosing neoplastic vessels are lined with atypical and proliferative active tumour cells with endothelial differentiation. In a recent extensive study of angiosarcomas of soft tissue, the morphological spectrum has been delineated and the striking variations of morphological features within a given neoplasm emphasised [7]. Frequently, a focal epithelioid cytomorphology characterized by abundant eosinophilic cytoplasm and vesicular nuclei with prominent nucleoli is seen in angiosarcomas of soft tissue [7]. However, purely epithelioid angiosarcomas are rather rare and easily mistaken for metastatic carcinoma [4].

Independently of clinical and morphological features, angiosarcomas are only very rarely confined to a pre-existing blood vessel, either because they do not arise from the endothelium of major vessels or because they destroy and invade so rapidly that angiocentricity cannot be verified [12].

Recently, we have seen three cases of intravascular epithelioid angiosarcoma.

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Materials and methods

The cases were identified in the consultation files of one of the authors (D.K.). The specimens were fixed in 10% buffered formalin, conventionally processed and embedded in paraffin wax. Sections 4 μm thick were stained with haematoxylin and eosin, periodic acid-Schiff reaction (PAS), and Goldner trichrome staining. Immunohistochemical studies were performed on paraffin sections with the alkaline phosphatase-anti-alkaline phosphatase method (APAAP) using appropriate positive and negative controls throughout. The antibodies used are listed in Table 1 with their dilutions and sources. Mitotic rate was expressed as the average mitotic count seen in 10 high-power fields (HPFs: 1 HPF=0.159 mm^2 for the microscope used); 30 HPFs were counted in each case. Clinical

Table 1 Antibodies used for immunhistochemical analysis (*ASMA* α-smooth muscle actin, *EMA* epithelial membrane antigen)

Antigen	Clone	Dilution	Source
Vimentin	V 9	1:40	Dako
CD31	JC/70 A	1:30	Dako
CD34	QBEND10	1:100	Dako
F VIII-antigen	F8/86	1:50	Dako
S-100 protein	Polyclonal	1:2000	Dako
Pancytokeratin	MNF 116	1:50	Dako
Actin	HHF 35	1:150	Dako
ASMA	1A4	1:80	Dako
EMA	E29	1:50	Dako

details and follow-up information were obtained from the hospital records, the laboratory request forms, and the referring pathologists if possible (see Acknowledgements).

Results

Case 1

A 61-year-old man had a 5-week history of initially transient, later progressive and permanent neurological deficit with right-sided hemiparesis and dysarthria. Magnetic resonance imaging showed an infarction in the parietal lobe. Duplex sonography of the left internal carotid artery revealed a poorly echogenic area, which was considered to be thrombotic material. Two weeks later a follow-up sonography demonstrated a dramatic increase of the "thrombus" formation described before. An operation was considered, and a preoperative angiography was performed (Fig. 1). At exploration after arteriotomy a very soft, red-brown material was found incompletely filling the lumen of the common and internal carotid artery below a stenosis at the probable upper end of a former endarterectomy (17 months ago). The internal carotid artery above and the common carotid artery below the bifurcation were resected over a length of 8 cm.

Histological examinations showed blood vessel structures with prominent fibrosis in the intima and media, foci of intramural haemorrhage and scattered inflammatory cells. Extensive arteriosclerotic plaques with focal calcification and cholesterol clefts were seen. In addition, malignant tumour tissue, which was limited mainly to the intima and showed infiltration of the media only focally, was identified. The neoplastic tissue was composed of large polygonal cells with abundant eosinophilic cytoplasm and vesicular nuclei with prominent nucleoli. These pleomorphic tumour cells were arranged in solid sheets or in a diffuse pattern with small holes and slits containing occasional erythrocytes (Fig. 2). The mitotic rate was increased to up to 5–6 mitoses/10 HPF, including atypical mitoses; foci of coagulative tumour necrosis were noted.

Imunohistochemical stains demonstrated vimentin positivity and a clear membranaceous positivity of tumour cells for CD31 (Fig. 3). Focally, tumour cells stained weakly positive for pancytokeratin. Stains with antibodies against CD34, factor VIII-related antigen, muscle-specific actin, and α-smooth-muscle actin were negative.

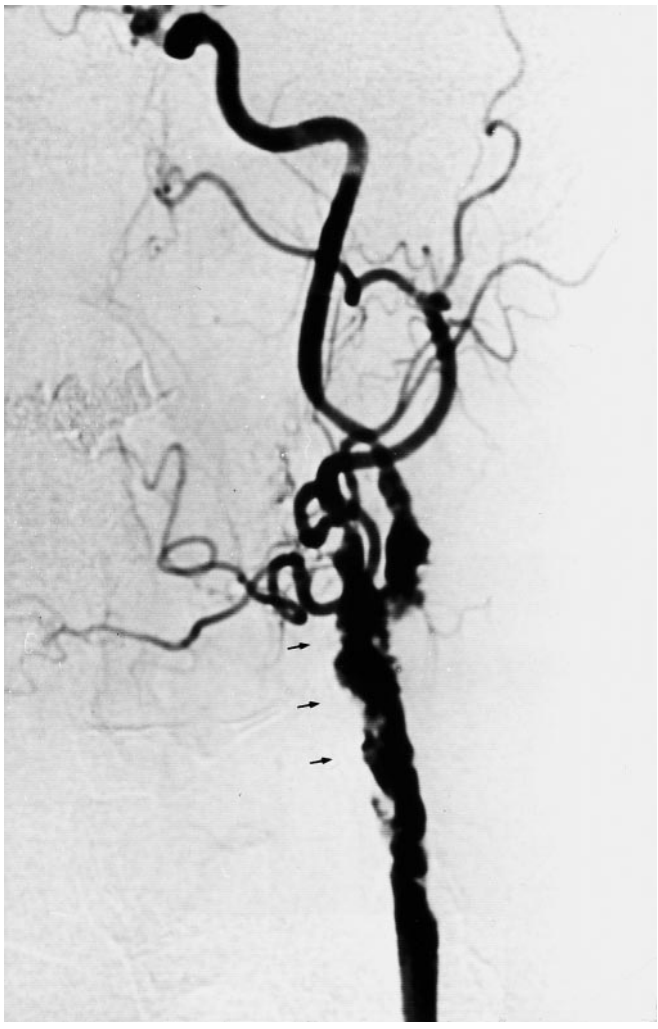
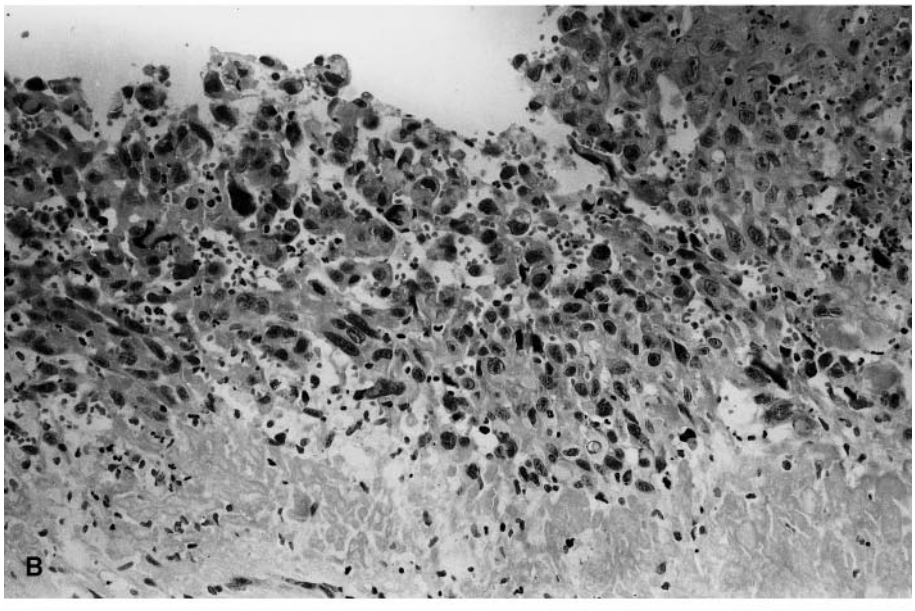


Fig. 1 Case 1: preoperative angiography revealing recurrent stenosis 17 months after endarterectomy, with an extended mural formation considered as "thrombotic" material (*arrows*)

The patient was checked carefully, but no other primary neoplasm was found by extensive clinical and radiological investigation. Up to 7 months after tumour excision no signs of recurrence or systemic metastases were noted.

Case 2

A 69-year-old female patient presented with high-grade stenosis of the infrarenal aorta and both renal arteries. Disobliteration was performed and histological investigation showed high-grade atherosclerosis with attached thrombotic material. Mainly on the surface of the thrombotic material and focally attached to the intima poorly differentiated malignant tumour tissue was identified. The polygonal epithelioid tumour cells showed a solid arrangement and contained enlarged round to oval vesic-



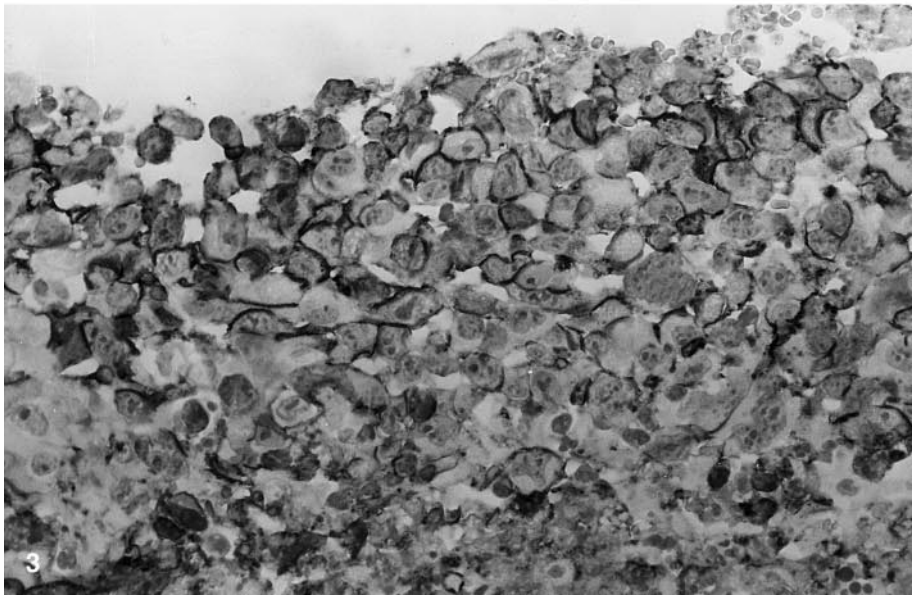


Fig. 2A, B Case 1. H&E **A** Blood vessel structures with prominent fibrosis and malignant tumour tissue limited to the intima. **B** At higher power pleomorphic epithelioid tumour cells with irregular nuclei are noted

Fig. 3 Case 1: immunohistochemically, a clear membranaceous positivity of tumour cells for CD 31 is seen. APAAP technique

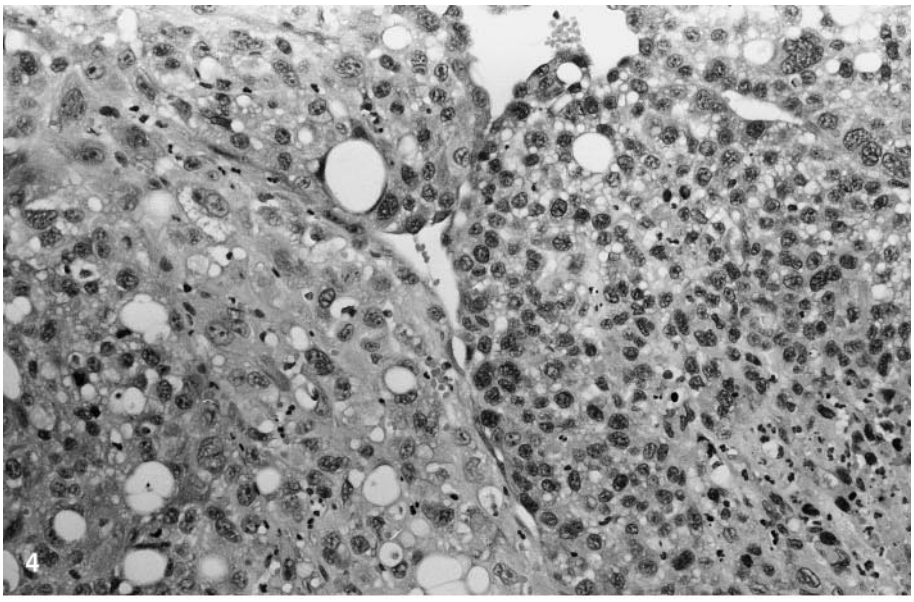


Fig. 4 Case 2: solid growth pattern of epithelioid tumour cells. Note cytoplasmic vacuoles in some cells. H&E

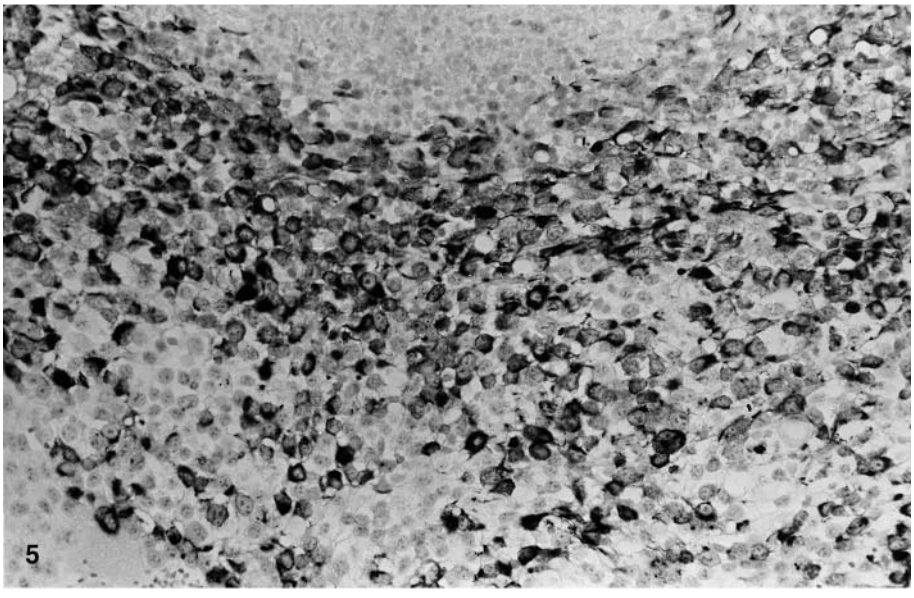


Fig. 5 Case 2: in addition to endothelial markers tumour cells stained positively for pancytokeratin. APAAP technique

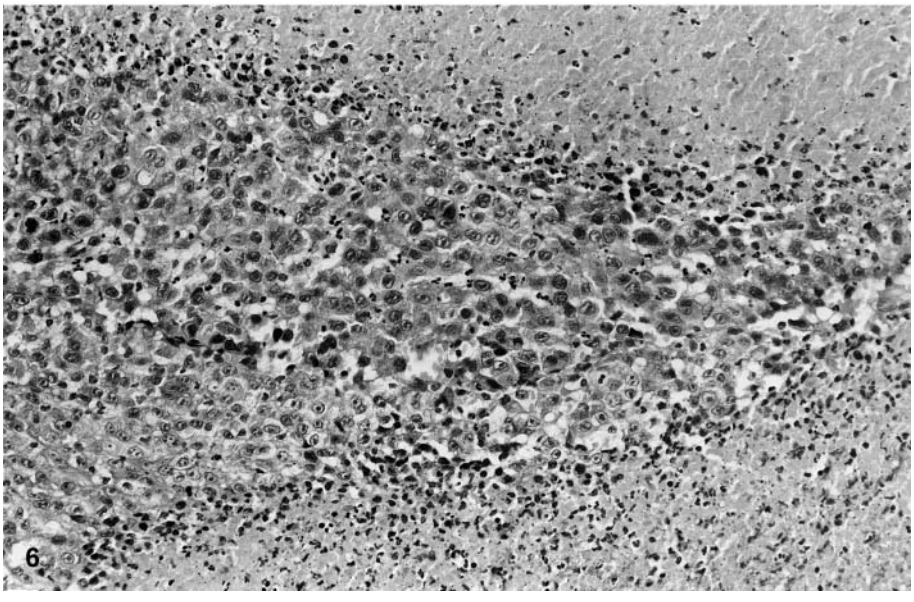


Fig. 6 Case 3: features of high-grade epithelioid sarcoma with extensive tumour necrosis are seen. H&E

ular nuclei with prominent nucleoli; multiple intracytoplasmatic vacuoles were identified (Fig. 4). Up to 4–5 mitoses per 10 HPF, including atypical mitoses and areas of tumour necrosis, were noted.

Immunohistochemically, tumour cells stained positively for vimentin, CD31 and factor VIII-related antigen; CD34 and UEA were only weakly positive. Most tumour cells also stained positively for pancytokeratin (Fig. 5), but were negative for epithelial membrane antigen (EMA).

The patient was checked carefully, but no other primary tumour or a soft tissue neoplasm invading the infrarenal abdominal aorta and renal arteries was present. A tumour recurrence developed at 6 months in the infrarenal abdominal aorta but not in the renal arteries. At the same time metastases were diagnosed in the left iliacal bone and in the right foot. Metastases in the anal and perianal region were found 10 to 11 months after excision of the primary tumour. Metastases in the backbone and spine were noted after 1 year.

Case 3

A 68-year-old male patient presented twice within 5 months with a recurrent stenosis of the abdominal aorta. Histological investigation of the resected material showed identical morphological features in both lesions. In addition to arteriosclerotic plaques and superficial intimal structures, high-grade malignant tumour tissue with extensive tumour necrosis was seen. Tumour tissue was composed of solid areas of pleomorphic epithelioid tumour cells containing enlarged round to oval vesicular nuclei with prominent nucleoli as well as occasionally intracytoplasmic vacuoles (Fig. 6). An increased mitotic rate with up to 10 mitoses in 10 HPFs was noted. Immunohistochemically, tumour cells stained positively for vimentin and CD31 and focally for pancytokeratin, while stains with antibodies against CD34 were only weakly positive. No other primary was found by careful clinical and radiological examination, and no signs of metastatic disease were present.

Discussion

Intravascular endothelial lesions almost always represent benign tumours or are reactive [12]. In decreasing frequency, intravascular endothelial lesions include papillary endothelial hyperplasia (so-called Masson's tumour), intravascular forms of pyogenic granuloma and epithelioid haemangioma. Occasionally angiosarcomas may arise at sites of altered vasculature (arteriovenous fistula/Dacron graft) [6] and in arteriovenous haemodialysis fistulas [2, 11]. In addition, epithelioid angiosarcoma has been reported to arise from pre-existing large blood vessels in rare cases [4, 5].

In the cases reported in this paper, characteristic histological and immunohistochemical features of epithelioid angiosarcoma, confined to the intima and adjacent parts of the media in case 1, were seen. No other primary neoplasm or a soft tissue angiosarcoma invading preexisting blood vessels was found. Therefore, the demonstrated lesions represent true intravascular angiosarcomatous neoplasms.

Primary sarcomas of large blood vessels are rare and represent leiomyosarcomas in most cases. In addition there is a small group of spindle cell sarcomas arising from the intima ("intimal" sarcomas) characterised by intimal endothelial, fibroblastic or myofibroblastic lines of differentiation [1, 5]. It seems therefore, that the reported cases represent a form of intimal sarcoma showing morphological features of epithelioid angiosarcoma similar to a previously reported case [5].

In the differential diagnosis a number of epithelioid neoplasms has to be considered, namely epithelioid haemangioendothelioma (EHE), metastatic carcinoma and malignant melanoma, epithelioid sarcoma, epithelioid leiomyosarcoma, and epithelioid malignant peripheral nerve sheath tumour (MPNST).

EHE is frequently associated with a vessel wall and in approximately 50% of cases its growth is angiocentric and angio-occlusive [8]. In contrast to epithelioid angiosarcoma, EHE is characterized by cytologically bland epithelioid endothelial tumour cells, which are arranged in nests and cords and set in a myxohyaline matrix.

Intravascular metastases of poorly differentiated carcinoma are the most common differential diagnosis of the tumours described in this paper. However, the convincing immunopositivity for endothelial markers and the negativity for epithelial membrane antigen are useful clues in the diagnosis of epithelioid angiosarcoma.

In contrast to metastatic malignant melanoma there was no nesting growth pattern, but tumour cells in our cases occasionally contained cytoplasmic vacuoles with erythrocytes. Immunohistochemically, tumour cells were negative for S-100 protein but stained positively for endothelial markers.

The coexpression of vimentin and cytokeratin in two of the cases reported raises the differential diagnosis of epithelioid sarcoma. Epithelioid sarcoma may display a pseudovascular pattern [10] and positive staining of tumour cells for CD34 [9]. However, the endothelial differentiation in our cases was clearly confirmed by strong positivity for CD31 in all cases.

Epithelioid changes may also occur in malignant smooth muscle tumours. Epithelioid leiomyosarcoma is mainly composed of epithelioid cells, although there are also small foci of spindle-shaped tumour cells in most cases. Immunohistochemically, epithelioid leiomyosarcomas stain clearly positive for muscular but not for endothelial markers.

A further differential diagnosis is metastatic epithelioid MPNST. The immunopositivity for S-100 protein and the lack of membranaceous staining for CD31 in epithelioid MPNST is of help in the distinction from epithelioid angiosarcoma.

In conclusion, the reported cases underline the fact that angiosarcoma may rarely arise within a pre-existing vessel.

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