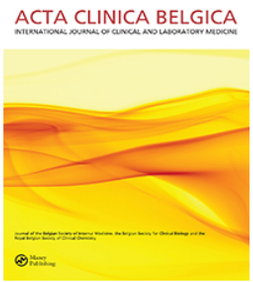

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CASE REPORT

Epithelioid angiosarcoma arising after an endovascular aneurysm repair: case report and review of the literature

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ABSTRACT

Objectives: We report the case of a 68-year-old male who was hospitalized for suspicion of endoleak and thrombosis of an aortic endoprosthesis, arising after multiple endovascular interventions during the last few months. During the intervention, amass was discovered, and biopsies were made. The anatomopathology results were in favor of an epithelioid angiosarcoma with atypical expression of CD31 and ERG– and no amplification of c-MYC. The main objective of this review is to highlight the difficulty of differential diagnosis, but also to evaluate overall survival according to treatments.

Methods: We performed a large review of the literature using PubMed for reports concerning angiosarcoma arising from Dacron grafts from 1981 to 2019. Articles presenting potentially relevant studies were read and analyzed.

Results: In our review, most of the patients were male (10 cases over 11 described), with amedian age of 63 years old (50–84 years old, 11 cases described). The overall interval time for the diagnosis after the endoprosthesis placement was 7.8 years (from 3.5 years to 17 years, 10 cases with the description) and the overall survival was 5 months (from 0 to 10 months, the only patient alive is not included, and only 8 cases had the description).

Conclusion: In most of the reviewed cases, there was no information concerning immunohistochemistry. Biopsies remain the standard for the diagnosis with immunochemistry and molecular test to avoid amisdiagnosis. Epithelioid angiosarcomas derived from Dacron grafts are a rare entity, which are difficult to diagnose because of the paucity of cases. Prognosis is poor, even if surgical option is possible.

KEYWORDS
Angiosarcoma; dacron grafts; primary angiosarcoma

Introduction

Sarcomas are rare, with an incidence counting for less than 1% of new cases per year (all histological subtypes of sarcomas included) [1].

Angiosarcomas (AS) belong to the vascular sarcoma group – the primary or de novo represents the majority of cutaneous and soft tissue AS and a proportion can be associated with foreign bodies (vascular grafts, prosthetic material) [2–6].

Secondary AS more frequently cutaneous are long-term sequelae of irradiation and/or lymphedema [6].

Angiosarcomas associated with Dacron grafts are more commonly epithelioid on histology, expressing CD31, ERG, Fli-1, MYC, variably pancytokeratin but without MDM2 or CDK4 expression.

These molecular and histologic testings are crucial to avoid confusion with metastatic carcinoma [7–18].

We herein report the case of a 68-year-old male who developed an epithelioid angiosarcoma after an endovascular aneurysm repair. Immunohistochemistry remains the key to distinguish angiosarcomas from other sarcomas or carcinomas.

Case report

A 68-year-old male was diagnosed with a left iliac artery aneurysm in 2015, with an estimated diameter of 5.6 cm. The patient had important cardiovascular comorbidities: ischemic cardiomyopathy, atrial fibrillation, obesity, high blood pressure. At this time, he underwent endovascular surgery with the placement of an iliac endoprosthesis and an embolization of the left external iliac artery. Three years and a half later, the patient developed claudication. The diagnosis of thrombus was done not only by echography but also with a computed-tomodensitometry (CT) scanner, and the patient benefits from endovascular stenting. Two months after the stenting, the patient developed a suspected endoleak with an increasing diameter of the known aneurysm and a compression of the psoas muscle.

Laboratory tests showed a C-reactive protein (CRP) at 112 mg/L (normal range: 0–10 mg/L), white cell level at 11,500/mm3 (normal range: 4000–11,000/mm3), neutrophils count at 8210/mm3 (normal range: 2000–7000/mm3), lactate dehydrogenase (LDH) level

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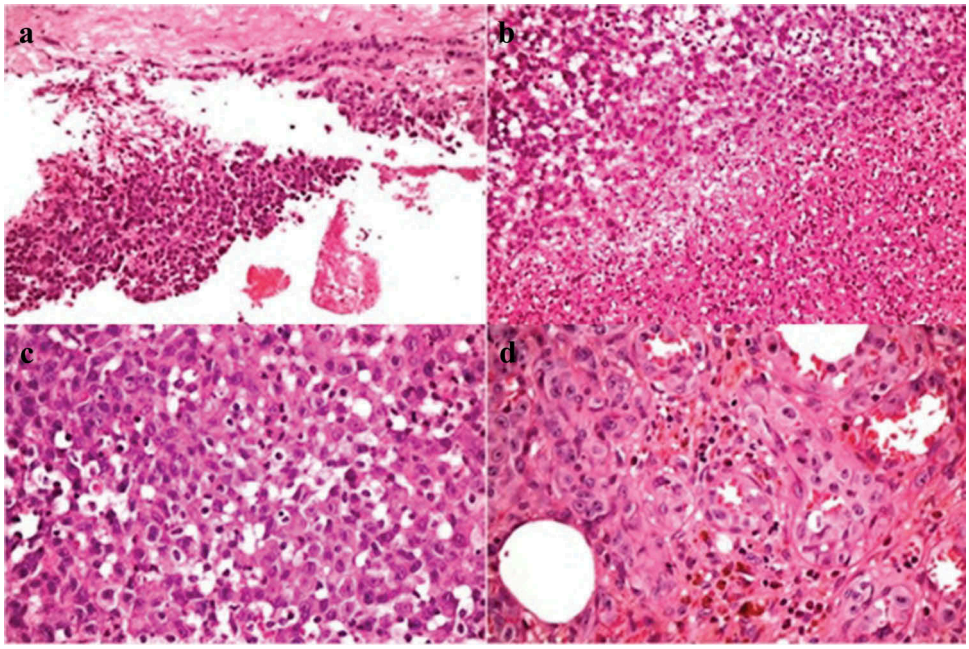

Figure 1. (a) Sheets of malignant cells attached to the wall of the prosthesis, (b) Necrotic material with sheets of malignant cells, (c) Sheets of malignant cells, (d) Vascular spaces lined by malignant cells.

at 248 U/L (normal range: 85–245). During that time, the patient has no pain but described loss of weight and food aversion. Because of the symptoms of weight loss, abnormal persistent CRP and LDH, a PET CT was done and showed an abnormal uptake in the area of the endoprosthesis and also in L5 which were both suggestive of an infectious complication. After 3 weeks of hospitalization, all the blood culture remained negative and unfortunately no bone biopsy was feasible. An aortic bypass was planned, but during the intervention, a suspicious mass was discovered. Biopsies were done and were compatible with an epithelioid angiosarcoma. The resected specimens consisted of a piece of the former prosthesis, an intraprosthetic thrombus and a biopsy of a mass in the scarpa region.

The former prosthesis revealed sheets of malignant epithelioid cells attached to its wall (Figure 1(a)). The intraprosthetic thrombus consisted of a necrotic mass containing sheets of malignant epithelioid cells (Figure 1(b,c)). As for the mass in the scarpa region, it was composed of vascular spaces lined by malignant cells and containing red blood cells (Figure 1(d)). The cells were strongly positive for CD31 (Figure 2(a)), ERG (Figure 2(b)), CD30 and pancytokeratin AE1/3 (Figure

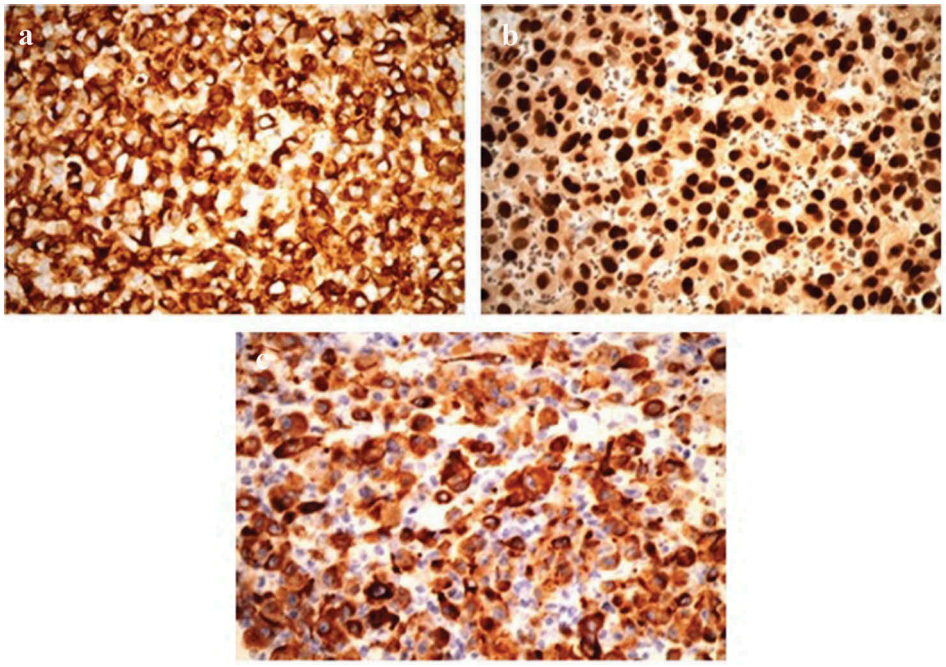

Figure 2. (a) Strong positivity for CD31, (b) Strong positivity for ERG, (c) Strong positivity for CKAE1/3.

2(c)) and negative for CD163, CD20, CD3, CD4, CD8, TIA, granzyme B, perforin and ALK. There was no c-MYC amplification. MDM2 and CDK4 were negative.

The patient underwent chemotherapy with Paclitaxel weekly, unfortunately, the treatment was prematurely stopped because of infectious complications. The patient died 5 weeks after the diagnosis and 3.5 years after the placement of the Dacron graft.

Discussion

Angiosarcoma is a rare entity which could be divided either as de novo (primary) or secondary [2–6].

Primary angiosarcomas are described as de novo or as associated with foreign bodies (as vascular grafts) and are the most frequently reported of cutaneous and soft tissue angiosarcomas. On histology, these angiosarcomas are most of the time epithelioid.

Secondary angiosarcomas are a consequence of long-term irradiation or chronic lymphedema [19].

We performed a large review of the literature (MEDLINE database) using PubMed for reports concerning angiosarcoma arising from Dacron grafts 1981 and 2019 mentioning MeSH terms 'angiosarcoma', 'dacron grafts sarcoma', and 'epithelioid angiosarcoma'. Articles presenting potentially relevant studies were read and analyzed (Tables 1 and 2).

In our review, most of the patients were male (10 cases over 11 described), with a median age of 63 years old (50–84 years old, 11 cases described). The overall interval time for the diagnosis after the endoprosthesis placement was 7.8 years (from 3.5 years to 17 years, 10 cases with the description) and the overall survival was 5 months (from 0 to 10 months, the only patient alive is not included, and only 8 cases had the description).

Differential diagnosis is difficult because of the unspecific symptoms, and the atypical clinical presentation of the cases. In our case, a prosthesis infection with osteomyelitis was at first suspected, as in the case of Fenton et al. [16]. In some cases, endoleak from the endoprosthesis can also be suspected. In all the described cases, symptoms are variable: claudication, unexplained fever, or loss of weight.

The diagnosis is also difficult to make because of the paucity of cases, and because of the misdiagnosis during the past years due to lack of precision of molecular analysis. To confirm the diagnosis, biopsies are essential to perform immunohistochemistry, cytogenetics and genetics sequencing and distinguish angiosarcomas from other type of sarcomas.

For the pathologist, the differential diagnosis of epithelioid AS arising from endovascular aneurysm included multiple hypotheses such as epithelioid hemangioendotheliomas (EHE), intimal sarcomas, metastasis from carcinomas, and secondary angiosarcomas.

Immunohistochemistry (IHC) analysis is essential for the correct diagnosis, and to avoid diagnostic pitfall.

EHE is a extremelyrare sarcoma which can be either indolent or aggressive. EHE is morphologically different from epithelioid AS. [20].

Table 1. Review of Agaimy et al. [7].

Authors and years	Age and gender	Type of grafts and underlying disease	Interval to angiosarcoma (years)	Treatment	Survival (months)	Histological pattern
Fehrenbacher et al. [8]	67 – M	Dacron Infra-renal aortic aneurysm	12 years	Resection of the graft	10	Angiosarcoma
Weiss et al. [9]	56 – M	Dacron Infra-renal aortic aneurysm	3.5 years	Resection and new graft, radiotherapy	Alive	Epithelioid angiosarcoma
Ben-Izhak et al. [10]	71 – M	Dacron Aorto-bifemorale disease	8 years	BSC	6	Epithelioid angiosarcoma
Okada et al. [11]	50 – M	Dacron Aortic root	17 years	Surgery	0.5	Epithelioid angiosarcoma
Umscheid et al. [12]	50 – M	Dacron Infra-renal aortic aneurysm	4.6 years	Surgery and chemotherapy	24	Epithelioid angiosarcoma
Almeida et al. [13]	60 – F	Dacron Right atrium	9 years	BSC	3 weeks	Angiosarcoma
Schmehl et al. [14]	84 – M	Dacron Infra-renal aortic aneurysm	8 years	Surgery and chemotherapy	NA	Epithelioid angiosarcoma

Table 2. Additional cases.

Authors and years	Age and gender	Type of grafts and underlying disease	Interval to angiosarcoma	Treatment	Survival (months)	Histological pattern
Moncure et al. [15]	?	Dacron Aorta	?	?	?	Angiosarcoma
Fenton et al. [16]	66 – M	– Infra-renal aortic aneurysm	6 years	Radiotherapy and chemotherapy	1	Angiosarcoma
Milite et al. [17]	60 – M	Dacron Abdominal aortic aneurysm	7 years	Surgery	Died at diagnosis	Epithelioid angiosarcoma
Tiwari et al. [18]	64 – M	Dacron AAA	?	Chemotherapy	?	Epithelioid angiosarcoma
Our case	68 – M	Dacron Infra-renal aortic aneurysm	3.5 years	Chemotherapy	1	Epithelioid angiosarcoma

Intimal sarcomas are high-grade malignant sarcomas arising in great vessels, especially pulmonary artery and aorta. Although highly pleomorphic, they display above all spindle cell morphology with sometimes a chondroid or myxoid differentiation. However, some of them can be confused with epithelioid AS. In these cases, the performance of MDM2 in IHC and in fluorescence in situ hybridization (FISH) is essential. Indeed, MDM2 overexpression in IHC is commonly observed in intimal sarcomas but also in rare cases of epithelioid AS but MDM2 amplification in FISH is only observed in intimal sarcomas [21,22].

At the same time, there was no MDM2 or CK4 expression, as in the three described cases of Agaimy et al. [7]. These results also support our diagnosis of AS. In fact, MDM2 overexpression is commonly observed in intimal sarcomas, but also in rare cases of AS while MDM2 amplification is only demonstrated in intimal sarcomas [21,22].

CD30 expression occurs in a significant subset of AS and EHE [23]. This expression induces a problem of differential diagnosis with other CD30-positive malignancies especially anaplastic large cell lymphomas (ALCL), some of which may be morphologically very similar to epithelioid AS, but also with some diffuse large B-cell lymphomas (DLBCL) and embryonal carcinomas. ALCL has more specific markers such as TIA-1 or granzyme, in addition to CD2 and/or CD4, which are not expressed in AS. DLBCL and embryonal carcinomas have also their specific markers such as CD20, CD79a and PAX5 for DLBCL and PLAP, SALL4 and OCT3/4 for embryonal carcinomas [24,25].

In sarcomas, MYC overexpression or inactivation are common and may distinguish sarcomas from a benign tumor. Two mechanisms exist for the overexpression: gene amplification or gene rearrangement, these are seen in angiosarcomas [26,27]. In our case, there was no overexpression of cMYC but a gain-function was detected in 92% of the cells. c-MYC amplification is most commonly seen in secondary angiosarcomas and rarely described in primary angiosarcomas [19,28].

In our case, the positivity of pancytokeratin, which is seen in carcinomas and in most cases of epithelioid AS, and the positivity of CD31 and ERG, which are more specific for angiosarcomas, confirmed the diagnosis of epithelioid AS [29,30].

The treatment of choice for soft tissue sarcoma is the surgical removal of the tumor. But in cases of advanced, unresectable, soft tissue sarcoma, chemotherapy is the standard of care with anthracycline-based chemotherapy. Doxorubicin alone or in combination can be used with Doxorubicin plus Ifosfamide. AS is very sensitive to taxanes, and in these subtypes, Paclitaxel or Docetaxel are options, alone or in combination with Gemcitabine [1]. Pazopanib could be an option in second-line treatment [31].

In our patient, weekly Paclitaxel was the first option because anthracycline-based chemotherapy was contra-indicated (chronic ischemic cardiomyopathy). The patient received only three cycles of weekly Paclitaxel (80 mg/m2) because of infectious complications and undergo palliative care.

In conclusion, AS derived from Dacron grafts are a rare entity, which are difficult to diagnose because of the paucity of cases. Prognosis is poor, even if surgical option is possible.

Disclosure Statement

No potential conflict of interest was reported by the authors.

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