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Angiosarcoma arising in association with vascular Dacron grafts and orthopedic joint prostheses: clinicopathologic, immunohistochemical, and molecular study☆,☆☆

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ABSTRACT

Angiosarcoma may rarely arise near an inert foreign body material including vascular grafts and metal joint prostheses. Sixteen such cases have been reported since 1972 but mostly in the radiologic or surgical literature without detailed histologic or molecular analyses. We herein describe the clinicopathologic and molecular features of 2 new cases and reanalyzed 3 previously reported cases of angiosarcoma that developed in association with Dacron grafts for vascular repair (n = 3) or related to orthopedic metal prostheses for joint replacement (n = 2). All patients were men aged 50 to 84 years (median, 71 years). Mean time to development of angiosarcoma was 9 years (range, 4.6-17 years). Symptoms were recurrent bleeding/loosening of prosthesis for suspected infection (in the joint prosthesis cases) and fatigue, weight loss, and abdominal symptoms in the Dacron-associated cases. Four patients died of disease within 1 to 24 months (mean, 8 months). One patient was alive after radical surgery, radiochemotherapy, and embolization of pulmonary metastases (17 months). Histologically, all tumors were high-grade epithelioid neoplasms with a predominant solid growth pattern and variable vasoformation. All tumors expressed CD31, ERG, FLI-1, and variably pancytokeratin (diffuse in 3 cases), but none expressed D2-40, MDM2, or CDK4. Fluorescence in situ hybridization analysis revealed no *MDM2* or *CDK4* alterations. MYC was expressed in all cases, but only 1 case was *MYC* amplified by fluorescence in situ hybridization. Angiosarcomas are exceedingly rare fatal complications of long-standing metal and Dacron prostheses. Awareness of their morphology and frequent cytokeratin expression is necessary to avoid misdiagnosis as metastatic carcinoma. Limited awareness of their existence explains delayed clinical diagnosis in most of cases. Absence of *MDM2*/*CDK4* alterations underlines their distinction from intimal-type sarcomas.

1. Introduction

Soft tissue sarcomas are uncommon (<1% of all cancer types). Angiosarcomas are even rarer representing less than 2% of all soft tissue sarcomas [1]. They mainly arise in the skin and superficial soft tissue and less frequently in deep soft tissue and bones [1]. Cutaneous angiosarcomas show a predilection for the head and neck skin, and they mainly affect the elderly [2]. On the other hand, deep-seated angiosarcomas mainly originate in the extremities, retroperitoneum, and trunk with a wide age range (5-97 years) [3]. Rarely, angiosarcomas may develop within visceral organs such as breast [4], liver [5], spleen [6], heart [7], kidney [8], gastrointestinal tract [9], urinary bladder [10], and abdominal and thoracic cavity including serosal membranes [11–13]. As is with soft tissue sarcomas in general, most angiosarcomas arise de novo without underlying systemic diseases or predisposing conditions. However, a subset of angiosarcomas arise in a background of previous irradiation for malignant diseases, in particular after breast-conserving surgery and adjuvant irradiation for breast cancer, prostate cancer, and others (secondary or postradiation angiosarcomas) [4,10]. Furthermore, angiosarcomas have been increasingly recognized to occur in specific predisposing clinicopathologic circumstances including well-documented cases related to exposure to chemical agents (liver angiosarcomas after thorotrast injection [5]), bullet and

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other war injuries [14], laparotomy sponge and other synthetic material left behind at surgical exploration [14,15], breast implants [16], injection site [17], gouty tophus [18] within chronic expanding hematomas [19], chronic lymphedema of diverse etiology [20], venous graft used as arterial bypass [21], and arteriovenous fistulae created for hemodialysis in patients with terminal renal failure [22]. Rare cases developed on a background of solid organ transplantation [23].

Angiosarcomas arising in association with Dacron grafts for vascular repair or related to orthopedic metal prosthesis for joint replacement are rare, with a total of 16 single-case reports published between 1972 and 2015 [24–39]. However, with 1 exception [28], all cases have been reported in the orthopedic, surgical, or radiologic literature, and hence, detailed histopathologic and immunohistochemical analyses were not provided. We herein describe 2 new cases of angiosarcomas arising in association with prostheses, reanalyzed 3 previously reported cases, and reviewed the literature to look for similar cases to delineate their major clinicopathologic features.

2. Materials and methods

Cases 1 to 3 have been reported previously [28,32,38,39]. Cases 4 and 5 were retrieved from the pathology departments of 2 of the authors (A.A. and B.P.R.). Tumor specimens were fixed in buffered formalin overnight and embedded routinely for histologic examination. Immunohistochemical stains were performed on freshly cut 3-μm paraffin sections using a fully automated slide preparation system ("Benchmark XT System"; Ventana Medical Systems Inc, Tucson, Arizona) and the following antibodies: pancytokeratin (clone KL-1, 1:200; Immunotech, Krefeld, Germany), cytokeratin (CK) 7 (OV-TL, 1:1000; Biogenex, Hamburg, Germany), CK20 (KS20.8, 1:50; Dako, Hamburg, Germany), ERG (clone EPR3864, prediluted/ready to use; Ventana Medical Systems), FLI-1 (clone G146-222, 1:200; BD Pharmingen, Heidelberg, Germany), podoplanin (clone D2-40, 1:50; Zytomed, Berlin, Germany), high-molecular-weight CK (clone 34ßE12, 1:50; Dako), SMARCB1 (INI1) (MRQ-27, 1:50; Zytomed), TP53 (clone DO-7, 1:50; Dako), MYC (clone EP121, 1:100; Epitomics, Burlingame, California), MDM2 (clone IF1, 1:50; CalBiochem, Pfullingen, Germany) and CDK4 (clone DCS-156, 1:100; Zytomed).

To detect amplifications of the *MDM2*, *CDK4*, and *MYC* gene loci, fluorescence in situ hybridization (FISH) was performed on freshly cut sections prepared from formalin-fixed, paraffin-embedded tumor tissue blocks using ZytoLight Dual Color Probes (ZytoVision, Bremerhaven, Germany) with standard protocols according to the manufacturer's instructions. Fifty tumor cell nuclei were assessed, and cases with a ratio greater than 2 were considered amplified.

3. Results

All patients were men aged 50 to 84 years (median, 71 years; Table 1). Three patients received Dacron grafts for vascular repair of the infrarenal aorta (2 cases) or of the right common iliac artery (one). Two patients received total hip endoprothesis for degenerative joint disease.

Mean time to development of angiosarcoma was 9 years and was similar for those with Dacron and joint prostheses (range, 4.6-17 years). Symptoms were unexplained recurrent bleeding/revision of prosthesis for suspected infection (in the joint prosthesis cases) and fatigue, unexplained weight loss, and/or abdominal pain in patients with Dacron-associated intra-abdominal angiosarcoma. Treatment was surgical resection and/or palliative radiochemotherapy in 4 patients. One patient refused any palliative therapy, and he died postoperatively of uncontrolled bleeding. Multiple pleural metastases were found at autopsy. Four patients died of disease (either with extensive metastatic disease or due to disease complications) within 1 to 24 months (mean, 8 months). One patient was alive after radical surgery, radiochemotherapy, and embolization of pulmonary metastases (last follow-up, 17 months).

3.1. Pathological findings

Angiosarcoma was closely associated with the implanted foreign body and formed a periprosthetic mass or capsule-like tissue variably encasing the prosthesis material or lining the original vascular lumen in the cases of Dacron grafts. A variable degree of osteolysis was seen on imaging of the joint prosthesis–associated cases (Fig. 1). Grossly, all tumors showed extensive hemorrhage closely mimicking expanding hematoma or infection at the time of revision. Histologically, tumor tissue was seen forming a capsule-like layer surrounding the joint capsule (Fig. 2A) or lining the original vascular lumen (Fig. 2B). All tumors were high-grade epithelioid neoplasms with predominant solid morphology and variable vasoformative component (Fig. 2C-E). The tumor cells were large with polygonal or rounded vesicular nuclei and prominent, centrally located nucleoli. The vasoformative component was generally minor and comprised less than 20% of the neoplasm (Fig. 2C). The solid tumor areas were strikingly reminiscent of poorly differentiated adenocarcinoma as several tumor cells contained empty intracytoplasmic vacuoles that occasionally looked like signet-ring cells or abortive gland formation (Fig. 2D). A corded pattern with voluminous cytoplasm occasionally containing single erythrocytes within vacuoles was seen as well (Fig. 2E). All cases showed variable stromal sclerosis with hemosiderin deposits as evidence of recurrent bleeding (Fig. 2F). Mitotic activity

Table 1
Clinicopathologic features of prosthesis-associated angiosarcomas (n = 5)[a]

No.	Age/sex	Site	Foreign body type	Time to angiosarcoma	Histology	Treatment	Follow-up
1	71/M	Aortobifemoral bypass. Tumor between graft and original right CIA	Dacron graft	8 y	Solid epithelioid, +gaping vessels	Palliative chemotherapy	DOD (6 mo)
2	50/M	Infrarenal aorta	Dacron graft	4.6 y	Solid epithelioid	Surgery + chemotherapy	Recurrence and lung MTS (12 mo); DOD (24 mo)
3	84/M	Infrarenal aorta	Dacron graft	8 y	Solid epithelioid, sclerotic areas	Surgery	Died postoperative. Lymph nodes and vertebral MTS
4	78/M	Hip, encasing the joint prosthesis	Total hip endoprosthesis	17 y. Revised after 14 y	Solid epithelioid, sclerotic areas	Palliative	DOD shortly after diagnosis
5	55/M	Left hemipelvis contiguous with prosthesis	Bilateral hip replacement	8 y	Anastomosing vessels, epithelioid cell features	Surgery + RCT	Lung MTS ANED (17 mo)

Abbreviations: ANED, alive with no evidence of disease; CIA, common iliac artery; DOD, died of disease; F, female; M, male; MTS, metastasis; RCT, radiochemotherapy.
[a] Cases 1 to 3 have been reported previously (see Table 3).