Malignant Aortic Tumors Following Open and Endovascular Implantation of Prosthetic Vascular Grafts

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Abstract

Objective: The aim of this study is to review the available literature on primary malignant aortic tumors following implantation of prosthetic vascular grafts.

Methods: A comprehensive literature search was obtained from MEDLINE via PubMed.gov, ScienceDirect.com, and Google Scholar using the following search queries: primary malignant tumors of the aorta; angiosarcoma of the aorta; aortic tumors vascular graft; angiosarcoma of the aorta Dacron graft; angiosarcoma of the aorta endovascular aortic repair; pseudoaneurysm or infection vascular graft; and pseudoaneurysm or infection endovascular aortic repair. In addition to the literature review, we report the case of a 59-year-old male who died of metastatic aortic angiosarcoma, following a staged replacement of the entire aorta using hybrid (combined open and endovascular) approaches.

Results: Our search produced 176 articles on primary malignant aortic tumors for review. We identified 18 publications on primary malignant aortic tumors following implantation of prosthetic vascular grafts, which included a total of 20 patients: 10 cases after open surgical implantation and 10 after endovascular stent-grafting. Our review showed that 9 of 20 patients (45.0%) with aortic tumors presented with a pseudoaneurysm or suspected graft infection. However, the prevalence of primary aortic malignancy in association with pseudoaneurysm or graft infection was only reported in these 9 cases.

Conclusions: Primary malignant aortic tumors are extremely uncommon, and are associated with very poor prognosis. The diagnosis should be considered in presence of a mass in association with a vascular prosthetic graft, especially if there is a pseudoaneurysm or periaortic inflammatory reaction. Further studies to search for the mechanisms involved in foreign body tumorigenesis in association with graft infection are still needed.

Keywords: primary aortic tumors; epithelioid angiosarcoma; Dacron vascular graft; endovascular stent-grafting; pseudoaneurysm; infection after endovascular aortic repair

Introduction

The aim of this study is to review the available literature on primary malignant aortic tumors following implantation of prosthetic vascular grafts. Previous publications on primary malignant aortic tumors following open surgical or endovascular implantation of prosthetic vascular grafts consisted of case reports. Primary angiosarcoma of the aorta is extremely uncommon, and is associated with very poor prognosis. It is characterized by rapid proliferation and propensity for metastatic disease, which leads to death in most patients.

Methods

A comprehensive literature search was obtained from MEDLINE via PubMed.gov, ScienceDirect.com, and Google Scholar using the following search queries: primary malignant tumors of the aorta; angiosarcoma of the aorta; aortic tumors vascular graft; angiosarcoma of the aorta Dacron graft; angiosarcoma of the aorta endovascular aortic repair; pseudoaneurysm or infection Dacron vascular graft; and pseudoaneurysm or infection endovascular aortic repair. PRISMA guidelines were used for the systematic review of the literature.

In addition to the literature review, we report the case of a 59-year-old male who died of metastatic aortic angiosarcoma 15-years following a staged replacement of the entire aorta using hybrid (combined open and endovascular) approaches. Our unusual case is what led us to review the available publications on malignant aortic tumors following open and/or endovascular implantation of prosthetic vascular grafts.

Statistical Analysis

Not applicable.
**Results**

Our literature search identified 176 articles for review on primary malignant aortic tumors. Only publications in English-language that included primary malignant aortic tumors following open surgical or endovascular implantation of prosthetic vascular grafts were selected (Figure 1). Patients with aortic tumors without prior vascular procedures, and tumor sites in peripheral vessels were not included in our review. A total of 18 publications, listed chronologically in Table 1, were selected for our review [1-18]. These consisted of case reports, which included a total of 20 patients: 10 cases after open surgical implantation and 10 after endovascular stent-grafting.

There was a significant male predominance (19 males and 1 female). The mean age at the time of diagnosis was 65.2 years (range 48 to 86 years), and the interval time from implantation of the prosthetic vascular graft to diagnosis of the malignant aortic tumor ranged from 4 months to 17 years (mean interval time 6.75 years). Fifteen of these tumors were located adjacent to a graft in the abdominal aorta, 3 in the descending thoracic aorta, 1 next to the aortic arch, and 1 attached to the aortic root. The most common histologic type was epithelioid angiosarcoma, which was diagnosed in 12 patients. Other histopathologic diagnoses were consistent with other types of sarcoma, including: intimal sarcoma (3 patients), malignant fibrous histiocytoma (3 patients), fibrosarcoma and leiomyosarcoma (1 patient each). Our review study showed that 80% of the patients (16/20) died after a reoperation or shortly after the diagnosis of aortic malignancy was made (range, 0 days – 2 years), and only 3 patients were alive after palliative chemotherapy, during a brief follow-up period ranging from 3 to 11 months. The outcome of 1 patient was not mentioned in one of the publications. 16 Diffuse metastatic disease was found in most patients.

Our review showed that 9 of the 20 patients (45.0%) diagnosed to have primary malignant aortic tumors following implantation of prosthetic vascular grafts presented with a suspected graft infection or a pseudoaneurysm. Three of these patients presented with a periaortic inflammatory mass at the site of previous Endovascular Aneurysm Repair (EVAR), two additional patients had a suspected endovascular graft infection, one patient developed a mass-like pseudoaneurysm after EVAR, and 3 patients had a pseudoaneurysm adjacent to a Dacron graft after open surgical implantation, also suspicious for graft infection [6,9,10,12,11,13,15,16,18].

However, we did not find any additional reports on malignant aortic tumors among 33 articles reviewed on pseudoaneurysms after open surgical implantation of Dacron grafts, and 53 articles reviewed on pseudoaneurysms after EVAR and Thoracic Endovascular Aortic Repair (TEVAR). Likewise, we did not find any additional reports on malignant aortic tumors among 106 articles reviewed on graft infection after open surgical implantation of Dacron grafts, and 21 articles reviewed on graft infection after EVAR or TEVAR.

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**Figure 1**: PRISMA flow diagram of the study
**Case Report**

A 59-year-old male with Marfan syndrome, who underwent emergent replacement of the ascending aorta for an acute type A aortic dissection in April 2001, when he was 44-years-old, presented with a 6.5-cm aneurysm of the distal aortic arch involving the origin of the left subclavian and left common carotid arteries in December 2001. The patient underwent a hybrid reconstruction of the aortic arch without using cardiopulmonary bypass, consisting of proximal reimplantation of brachiocephalic vessels, combined with endovascular implantation of a thoracic endovascular stent-graft to exclude the entire aortic arch. The technical details of this novel procedure were reported by our group in 2003 [19]. The patient subsequently underwent multiple vascular procedures, which were previously described in a separate publication 2017 [20]. Of special interest is the fact that our patient underwent a staged replacement of the entire thoracic and abdominal aorta using hybrid (combined open and endovascular) approaches. In addition to the hybrid reconstruction of the aortic arch in 2001, the patient underwent a hybrid reconstruction of a thoracoabdominal aorta in 2008, consisting of open replacement of the suprarenal abdominal aorta and debranching procedure to celiac, superior mesenteric artery and both renal arteries, combined with TEVAR of the thoracoabdominal aortic aneurysm.

The patient was reevaluated in December 2016, 15-years after he underwent off-pump hybrid reconstruction of the aortic arch. He presented with low back pain and a new mass in the left neck, which was neither tender nor pulsatile on exam. Computed tomography of the neck, chest, abdomen and pelvis revealed a conglomerate of enlarged left cervical, axillary, mediastinal, subcarinal and retroperitoneal lymph nodes, in addition to multiple bilateral lung nodules, and lytic lesions in T11 and T12 vertebrae, likely representing metastatic disease (Figure 2). A needle biopsy of the left neck mass showed a dyscohesive population of large, highly atypical epithelioid cells with abundant cytoplasm and enlarged irregular nuclei with prominent nucleoli, with immunohistochemistry positive for vascular markers ERG and CD31, consistent with epithelioid angiosarcoma (Figure 3). His clinical course was complicated with progressive respiratory failure, and the patient expired.

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**Figure 2:**
(A) Computed tomography of the neck after administration of intravenous contrast showing left cervical and left supraventricular lymphadenopathy, with increased number of abnormally rounded and enlarged lymph nodes in the lateral view.
(B) Computed tomography of the chest, revealed a conglomerate of enlarged axillary, mediastinal and subcarinal lymph nodes, in addition to multiple bilateral lung nodules.
(C) Computed tomography of the chest, abdomen and pelvis showing destructive lytic process of T11 and complete loss of height of T12 vertebral body, likely representing metastatic disease.

T11 = eleventh thoracic vertebra. T12 = twelfth thoracic vertebra.
Figure 3: (A) Fine needle aspiration of cervical lymph node (pre-mortem). The smears showed a dyscohesive population of large, highly atypical epithelioid cells with relatively abundant, occasionally vacuolated, cytoplasm. The nuclei are enlarged, round to irregular, with prominent nucleoli, intranuclear inclusions and coarse chromatin. Intracytoplasmic lumina containing erythrocytes are also present. (Diff-Quik stain, 400 x magnifications). (B) Fine needle aspiration of cervical lymph node (pre-mortem). The diagnosis of epithelioid angiosarcoma was confirmed by positive immunohistochemistry for vascular markers ERG and CD31. (Immunohistochemistry, 400 x magnifications). CD31 = Cluster of Differentiation 31, ERG = Erythroblast transformation-specific Related Gene.

Histopathologic Findings on Autopsy

Only a limited autopsy was authorized by the patient’s wife. The resected tumor at autopsy revealed predominantly soft necrotic tissue. On histological evaluation, the tumor was an epithelioid angiosarcoma consistent with the pre-mortem fine needle aspiration of his cervical neck mass. The tumor showed marked tissue necrosis with largely dyscohesive high-grade pleomorphic epithelioid cells with prominent irregular nuclei with intranuclear inclusions. Some of these cells contained intracytoplasmic lumina. The cytoplasm frequently was vacuolated (Figure 4).

Figure 4: (A) Cervical mass resection (post-mortem). The tumor consists of dyscohesive high-grade epithelioid cells with prominent nuclei, with marked background necrosis. (hematoxylin and eosin stains, 200x magnification). (B) Cervical mass resection (post-mortem). The malignant high-grade epithelioid cells exhibit vacuolated cytoplasm (arrows). (hematoxylin and eosin stains, 400x magnification). (C) Cervical mass resection (post-mortem). Some of malignant high-grade epithelioid cells contain intracytoplasmic lumens with erythrocytes (arrows). (hematoxylin and eosin stains, 400x magnification).
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Discussion

Primary malignant tumors of the aorta are very uncommon, and since their first report in the literature in 1873 by Brodowski, only 140 cases have been reported [14]. Only 35 cases of primary aortic angiosarcoma were reported in the literature, representing 25% of all the primary aortic malignancies [14]. Aortic angiosarcoma is an aggressive malignancy with significant metastatic potential and very poor prognosis, with survival ranging from 1 week to 22 months after the diagnosis [14]. The association of primary sarcomas of the aorta arising from previously implanted Dacron vascular grafts was first recognized by Burns and coworkers in 1972, who described a rapidly growing fibrosarcoma in the left groin of a 31-year-old man, originating at the site of a woven Dacron graft implanted in the femoral artery 10 years earlier [21].

It had been postulated in experimental studies that malignant tumors may develop after implantation of foreign bodies. Oppenheimer and colleagues demonstrated the induction of fibrosarcoma developing in the fibrous capsule around implanted plastic discs in animals [22]. Studies by Brand and associates and Karp and colleagues suggested that implanted material may be tumorigenic if the size of the pores of is too small [23,24]. Both studies have demonstrated that if the pore size was less than 0.4 μ and 0.2 μ, respectively, the implanted discs were carcinogenic, because they prevented cellular invasion, and sarcomatous transformation may initiate in the fibrous capsule. Although the production of tumors through solid-state mechanisms had been demonstrated in experimental animals, foreign body tumorigenesis has not been proven definitively in man. The association of angiosarcoma with foreign body material (including a retained bullet, a laparotomy sponge, and bone wax used for hemostasis in a bone graft donor site) was described in 3 cases by Jennings and coworkers [25]. In their review, the authors also identified 6 cases of angiosarcoma and 40 cases of sarcomas of other histologic types associated with foreign material, with latency periods of from 4 months to 63 years. They concluded that implanted foreign material should be considered capable of inducing virtually any form of sarcoma in humans.

Although several reports have described the association of primary aortic tumors following implantation of Dacron vascular grafts, mechanisms by which these neoplasms arise and the role the grafts may have in carcinogenesis have yet to be elucidated [13]. Ben-Izhak and collaborators suggest that dense fibrous tissue with traces of chronic inflammatory response around the graft and, for unknown reasons, the cells in this inflammatory process may undergo a malignant transformation, probably associated with oncogene activation and tumor suppressor gene inactivation [7].

Several investigators have reported cases of aortic angiosarcoma in patients with suspected endograft infection [10-13,18]. This is concerning because endograft infection, although rare, may be a predisposing condition for malignant transformation. While causality cannot be proven, these malignancies were not present at the time the graft was implanted using open surgical technique, and were not suspected either at the time of endovascular graft insertion. Furthermore, these tumors originated from the aortic wall adjacent to the graft [9].

Immunohistochemical studies of an inflammatory mass attached to an endograft performed by Garg and colleagues revealed reactivity for CK7, CD31 and FLI-1, supporting the diagnosis of mesenchymal neoplasm with aberrant keratin expression, consistent with intimal sarcoma [12]. In another study, Stewart and associates carried out a selected immunohistochemical analysis that combines both the application of phospho-specific probes directed against putative sites of activation on protein analytes and cellular compartmentalization in an attempt to define the possible molecular mechanisms of tumorigenesis and the chemo-resistance of such tumors and to uncover potential therapeutic applications for the patients. Their findings support the roles for those pathways in the biology and development of high-grade sarcoma of aorta, and thus, these pathways may represent potential therapeutic targets.

Our review showed that 9 of 20 patients (45.0%) who presented with suspected graft infection or pseudoaneurysm were eventually diagnosed to have a primary aortic malignancy in association with a prosthetic vascular graft. Of these, 3 patients presented with a peri-aneurysm inflammatory mass at the site of previous Endovascular Aneurysm Repair (EVAR), two additional patients had a suspected endovascular graft infection, one patient developed a mass-like pseudoaneurysm after EVAR, and 3 patients had a pseudoaneurysm adjacent to a Dacron graft after open surgical implantation, also suspicious for graft infection [6,9,10,11,12,13,15,16,18]. It appears, thus, that the presence of graft infection or peri-aneurysm inflammation may represent an incremental risk for malignant transformation. Nevertheless, the association between malignant aortic tumors and pseudoaneurysm or graft infection after open or endovascular implantation of prosthetic vascular grafts may be random rather than causal [17].

Conclusions

In summary, our systematic review identified 18 publications on primary malignant aortic tumors following implantation of prosthetic vascular grafts, which included a total of 20 patients: 10 cases after open surgical implantation and 10 after endovascular stenting [1-18]. The tumorigenic potential of implanted foreign material Dacron grafts has been suggested in previous animal and human studies. Although the prevalence of aortic malignancies in association with prosthetic vascular grafts is extremely low among thousands of patients in whom these devices were implanted, the likelihood of carcinogenesis may be increased in the presence of graft infection or peri-aneurysm inflammation. Further studies to search for the mechanisms involved in foreign body tumorigenesis, in association with graft infection are still needed.
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Declarations

Conflict of Interest Declaration

The authors have no conflicts of interest to disclose with any financial/research/academic organization, with regards to the content/research work discussed in the manuscript.

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The authors have not received any payments or services, either directly or indirectly from a third party in support of any aspect of this work.

Ethical Approval

According to the policies of the Institutional Review Board (IRB) at the University of New Mexico, this study does not require review by the institutional Human Research Review Committee (HRRC).

References


