Case Report

Recurrent leiomyosarcoma presenting as malignant arterial tumor thrombus

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Introduction

Cervical sarcomas make up less than 1% of all cervical malignancies and cervical leiomyosarcoma (LMS) constitutes a percentage of that group (Khosla et al., 2012). Given the rarity of this condition, much about cervical LMS has been extrapolated from the uterine LMS literature and isolated case reports and case series (Khosla et al., 2012). Uterine LMS has a poor prognosis with a median reported survival of 10 months, a five-year overall survival (OS) of 51% and 25% for stages I and II respectively and a recurrence rate ranging from 53 to 71% (McDonald et al., 2007). In general, cervical sarcoma has been shown to have similar outcomes to uterine sarcoma with a five-year OS reported as 67–80% for stage I disease and a five-year OS of 20% for stage II (Khosla et al., 2012). The infrequency of cervical LMS limits our insight into recurrence rates and patterns.

Vascular invasion with subsequent tumor embolization by LMS is rare (McDonald et al., 2007). Intravascular invasion of the benign counterpart, leiomyoma, is well-described in the literature as intravascular leiomyomatosis (McDonald et al., 2007). Although pulmonary tumor embolus has been described, no cases exist in the current literature of malignant arterial tumor embolus (MATE) of LMS to the lower extremities with resultant claudication (McDonald et al., 2007). Furthermore, no reports have featured MATE as the initial presentation of tumor recurrence. We present the first case of malignant tumor embolus of LMS to the popliteal artery, thereby highlighting the importance of considering a metastatic work-up in a patient with acute vascular thrombosis and a history of malignancy.

Case report

A 53-year-old woman with a history of Stage IB2 high-grade cervical leiomyosarcoma 5 years prior presented to an outside hospital describing three weeks of dyspnea and the acute onset of left lower extremity (LLE) pain, coldness and paresthesia. Her cancer was primarily treated with a radical hysterectomy and bilateral salpingo-oophorectomy followed by 6 cycles of gemcitabine and docetaxel. Post-treatment evaluation showed no evidence of disease. Otherwise, her medical history was notable for diabetic vasculopathy resulting in the amputation of her right third toe due to chronic infections. She had no history of thromboembolic events or claudication. Subsequent to treatment, the patient was lost to follow-up until re-presenting with her recurrence.

A doppler ultrasound of the LLE revealed an ankle-brachial index (ABI) of 0.34, compatible with severe ischemia due to an obstructive popliteal artery thrombus. She underwent an emergent popliteal endarterectomy. Histopathologic examination of the extracted thrombus demonstrated a high-grade leiomyosarcoma that was diffusely positive for desmin, smooth muscle actin (SMA) and p16, favoring smooth muscle origin of the tumor cells (Fig. 1). Computed tomography (CT) of the chest, abdomen and pelvis also demonstrated multiple large pulmonary metastases in the bilateral lung fields. The abdominopelvic portion of the CT showed no intra-abdominal foci of recurrence and no obvious source of the left popliteal thrombus. The patient was discharged from the hospital on therapeutic enoxaparin anti-coagulation. She was re-treated with gemcitabine and docetaxel, with a mixed response, and is now enrolled in a clinical trial.

Discussion

Malignant arterial tumor embolization (MATE) is a rare complication of malignancy described most commonly in the setting of primary pulmonary carcinomas and sarcomas (Chandler, 1993). These embolizations usually occur peri-operatively or immediately post-operatively (Chandler, 1993). Thus far, MATE as the presenting sign of recurrent leiomyosarcoma has not been reported in the literature; however, several circumstances surrounding this patient's...
malignancy may place the patient at particularly high risk for developing this condition.

Venous thromboembolism (VTE) is the second leading cause of death in patients with a malignancy (Furie and Furie, 2008). Cancer is also a risk factor for VTE development due to pro-thrombotic factors such as tissue factor and Factor VIIa (Furie and Furie, 2008).

Arterial thrombosis is less common than venous thrombosis in patients with cancer (Khorana et al., 2008). Unlike VTE, however, the mechanism and underlying pathophysiology of malignancy and arterial thromboses are less clearly defined. Arterial thrombosis is commonly described in the context of atherosclerotic disease leading to ischemic stroke or myocardial infarction. While there are some physical similarities such as damage to the vascular endothelium causing platelet activation and subsequent thrombosis, the rarity of this vascular event suggests that additional mechanisms are needed for arterial thrombus formation and/or embolization.

Specifically, acute arterial occlusion of the lower extremities has been associated with atherosclerosis, inflammation, trauma and thrombus associated with exogenous graft placement (el-Shami et al., 2007). Of note, the most common thrombosis sites have been reported to be in the spleen, kidney and extremities, presumably due to both mechanical forces and resultant growth factor release (el-Shami et al., 2007). Other than atherosclerotic lesions, arterial thrombus is most commonly associated with direct vessel trauma leading to platelet activation and subsequent thrombosis, the rarity of this vascular event suggests that additional mechanisms are needed for arterial thrombus formation and/or embolization.

Our patient presented with near complete occlusion of the popliteal artery. In this case, the presence of LMS in the popliteal artery appears to be a recurrent metastatic focus. Due to the rarity of this entity, the pathophysiology of a malignant tumor embolus in the setting of recurrence is unclear. However, given our understanding of the factors leading to thrombosis, the idea of tumor thrombus as a recurrence is biologically plausible.

Since cancer cells can be found in human circulation without radiographically detectable metastases, gross metastasis appears to depend on a specific interaction between the cancer cell and the microenvironment distant from the primary tumor (Chiang and Massague, 2008). Several growth factors also appear important for metastasis and growth (e.g., matrix metalloproteinases, cyclooxygenase-2, and epidermal growth factors) (Chiang and Massague, 2008). Although the mechanism remains poorly understood, individual tumor cells harbor the potential to lie quiescent and, later, enter a proliferative state once they acquire the necessary characteristics, such as angiogenesis promotion (Almog, 2010). Some have postulated a possible interaction between the arterial vessel wall and dormant tumor cells that leads to proliferation and, ultimately, thrombosis (Hibino et al., 2012). In cases of pulmonary tumor embolism (PTEM), Hibino and colleagues hypothesize that tumor cells obstruct small pulmonary arteries leading to cell-mediated immune response causing intimal proliferation and larger thrombosis (Hibino et al., 2012). Although plausible for pulmonary tumor emboli, the same mechanism may not apply to larger peripheral vessels such as the popliteal artery. Since oxygen levels vary depending on which human tissue is studied, increased hypoxia in unexpected hypoxic regions may trigger HIF1-α, an important pro-angiogenic, anti-apoptotic factor (Chiang and Massague, 2008). This mechanism may be a contributing factor to the development of cancer recurrence and metastasis specifically in tissue with less oxygenation such as in the extremities, as seen in our patient.

Vasculature involvement by sarcomas has been reported. A PubMed search (1993–2012) for “sarcoma” and “embolism” revealed 14 citations involving arterial embolism with only two cases of peripheral arterial emboli. No cases of LMS or arterial emboli presenting
as a recurrence were listed. One case of a woman with a breast fibrosarcoma presented with bilateral lower extremity ischemia. She was found to have bilateral femoral artery occlusion with tumor emboli consistent with her primary breast pathology. Similar to our case, she was found to have pulmonary metastasis, however, this entire presentation occurred within 2 weeks of her original surgery (Lacroix et al., 1994). This patient died 2 months following her MATE diagnosis. There were no cases representing MATE as a recurrent presentation.

Although leiomyosarcomatosis has been described in the literature, it presents as a direct extension into arterial/venous vasculature from the primary tumor (McDonald et al., 2007). To our knowledge, this is the first reported case of tumor embolus of leiomyosarcoma to the popliteal artery. Our patient had a history of cervical leiomyosarcoma five years prior, thus a recurrence in the lower extremity and lungs was the most likely diagnosis. The diagnosis of recurrence is more likely than a diagnosis of a new primary vascular leiomyosarcoma.

In patients with a history of leiomyosarcoma presenting with acute arterial thrombosis, MATE should be considered in the differential as a possible etiology of the thrombus. Inability to recognize the etiology of ischemia can have catastrophic consequences including the possibility of limb loss or death (Chandler, 1993). Specifically, this case exposes a unique presentation of recurrent disease. The mechanism of this phenomenon remains unclear and warrants further investigation. Patients with risk factors for thromboembolic events, such as cancer, should be considered candidates for indefinite anticoagulation therapy.

Conflict of interest statement
The authors have no financial conflicts of interest to disclose.

References