Malignant Fibrous Histiocytoma of Vagina Radiation-Induced in a Patient with Squamous Carcinoma of Uterine Cervix: Case Report and Review of the Literature

Montserrat Grau Bono*
Department of Gynecology and Obstetrics, Hospital General d’Ontinyent, Departament de Salut Xativa-Ontinyent, Valencia, Espana, Spain

Introduction

Malignant fibrous histiocytoma (MFH) represents a common, aggressive, soft tissue sarcoma of adulthood. However, for some authors, MFH is a term for poorly differentiated sarcomas of a variety of different phenotypes, or a distinct clinicopathologic entity [1].

The malignant fibrous histiocytoma was initially described by O’Brien and Stout in 1964. Though MFH represents approximately 30% of all soft tissue sarcomas, annual incidence is estimated to be only 0.42 per 100,000, with diagnosis peaking in the fifth to sixth decade. MFH usually involves the lower (49%) or upper (19%) extremities, retro peritoneum (16%), or head/neck and trunk (16%). Intra-abdominal MFH is rare, as is MFH of the Müllerian tract, though few cases involving the vagina and paravaginal space have been described [2,3]. Malignant tumors originated in vagina account for only about 1% of all gynecological tumors, and gynecological sarcomas in themselves, are extremely rare [4].

MFH represents an aggressive neoplasm with unique molecular, immunohistochemical, and behavioral characteristics. Most MFHs arose de novo; however, a minority developed as a long-term sequela of radiation [1].

Post-irradiation sarcoma (PRS) is extremely rare and accounts for 0.5-5.5% of all sarcomas and the most frequent histological subtypes are MFH, angiosarcoma, leiomyosarcoma and fibrosarcoma [5].

Risk factors for development of MFH have not been well characterized. MFH develops mutations following exposure to ionizing radiation, th us linking prior radiation therapy as a likely risk factor in some cases. In fact, MFH is the most commonly diagnosed sarcoma in patients with prior radiation exposure in the head or neck region, with radiation-associated tumors in this area carrying a worse prognosis than those arising without proceeding. Furthermore, the radio-induced HFM have a worse prognosis than those not associated with RT [6].

Macroscopically the MFH of the vagina are usually large lesions due to rapid growth, of soft tissue, smooth surface and sometimes bleeding. Histologically, the tumors consist of a pleomorphic spindle and histiocytic cell population. There are often associated regions of hemorrhage and necrosis, and an associated lymphohistioscytic infiltrate.

Keywords: Malignant fibrous histiocytoma, Sarcoma radiation-induced
is not uncommon. Individual tumor cells are markedly atypical, often quite large, and frequently exhibit numerous and irregular mitotic figures [1, 6].

Although the histology may provide clues for differentiating MFH from other tumors, the effective use of immunohistochemistry has become critical for arriving at the correct diagnosis.

**Case Report**

A 64 year-old Caucasian woman presented with a one month history of vaginal bleeding intercourse. The patient had six vaginal deliveries.

At age 34, she underwent a simple total hysterectomy due to metrorrhagia, initially, without suspicion of malignancy. The study of the surgical specimen showed a cervical squamous cell carcinoma moderately differentiated, and the later extension study showed a tumor FIGO stage IB-2 with pelvic lymph nodes affected.

The treatment was completed with pelvic radiotherapy with Co-60, receiving a RT total dose of 4950 rad. Further gynecological and cytological controls were correct.

Now, 30 years after hysterectomy and radiotherapy, the gynecologic exam reveals the vagina occupied by exofitic and bloody tumors depend on the wall of the vagina. The patient doesn’t experience local pain and her general conditions are right.

These lesions were resected vaginally. The pathology reports out at macroscopic level three white nodular fragments with a smooth surface tissue with a dimension of 5x4x2.5 cm.

Cytological diagnosis of a sample of the tumor surface showed large atypical cells and multinucleated giant cells with rough, granular, chromatin and notable nucleoli. Histopathology analysis of the biopsied tissue sample confirmed inflammatory cells infiltration, with polymorphic and fusiform cells that resembled fibroblasts, appearing as though they were entangled bundles, exhibiting a storiform. Higher magnification showed polymorphic and atypical cells. The expression of mitotic index was 11 mitoses per 10 high power fields and the expression of proliferative index was Ki-67: 75%. Immunohistochemical standing showed positive reactions to: α-smooth muscle actin (α-SAM), S100 (marked to Schwann cells) in few scattered cells, CD31 and CD34. However, results were negative for caldesmon, desmine and CD56.

The computerized tomography showed absence of distant metastases.

Three weeks after the resection, the vagina was occupied by a new exofitic and bloody mass of similar characteristics to the previous one.

Under this aggressive situation, the patient was treated with a new vaginal resection of the vaginal lesions, pelvic and intracavitary radiotherapy and chemotherapy.

Nowadays, 4 years later, the patient remains free of disease.

**Discussion**

Radiotherapy is significantly used in the treatment of various cancers as well as in treating benign and inflammatory diseases. Adjuvant RT is also widely administered to limit the extent of surgical resection, prevent local recurrence, and improve functional and cosmetic outcome in some tumors like breast, rectal, and musculoskeletal tumors. Approximately 35% of all patients with cancer will receive RT during the course of their disease [7]. Its use is associated with toxicity, such as impaired wound healing, anastomotic breakdown, fibrosis, and joint stiffness. However, an ominous sequel that manifests years after therapy is the development of a secondary malignancy. Soft tissue sarcomas are one of the most common types of radiation-associated tumors; the post-radiation sarcomas (PRS) are a potential late sequel of RT with a reputation of aggressive pathology and poor outcome. Post-irradiation sarcomas affect all age groups [5, 7].

Patients irradiated for cancer of cervix are frequently followed for later development of second cancers; as treatment is relatively successful and patients survive long enough to be at risk for late complications of RT. The association of RT with risk of second cancer depends on age at the time of diagnosis; younger patients of cancer of cervix have high risk for second cancer [5].

According to Lagrange et al., the criteria required for PRS are: different histological features of the primary lesion and the PRS; sarcoma arising within the irradiated field; and a latent period of at least 3 years. The latent period between initiation of RT and diagnosis of second cancer ranges from 7 to 45 years (mean 16.8 years) [5, 8].

As the prognostic factors we can define: the histological type (leiomyosarcoma, fibrosarcoma and myxofibrosarcoma have better prognosis), the tumor size (lesions ≥ 10 cm have worse prognosis, because there is less resectability), the histological grade, the presence of necrotic tissue, the higher proliferative index, some genetic factors and the poor response to CT or radio-resistant tumors, which also indicate poor prognosis.

MFH tends to be locally and hematogenously aggressive. Metastatic rate varies with histological subtype: giant cell (50%), storiform/pleomorphic (20-65%), myxoid (23-30%), and inflammatory (25-30%) [1, 3].

After diagnosis, further investigation may be helpful to delineate the extent of local invasion and to assess for metastatic disease. Recent studies have reported certain magnetic resonance imaging (MRI) features favoring metastasis that include heterogeneous signaling on T2-weighted images, perilesional edema, and tumor necrosis. Sentinel lymph node biopsy has been suggested as an effective method for evaluating regional disease, perhaps in light of an early autopsy study describing lymph node metastasis in 50% of patients who had died from MFH. However, other more recent studies, have reported lymphatic involvement in as few as 2.6% of cases, and the utility of the procedure has yet to be conclusively demonstrated. Positron emission tomography/computed tomography scanning may also be employed to assess for metastases [9-13].

Radical surgery is the only treatment to improve disease-free survival. Unfortunately, obtaining sufficient margins has often led to extensive reconstructive challenges amidst high local recurrence rates, which have been reported to range from 19% to 66%. Current practice typically consists of en bloc resection with an approximate 2 cm margin of uninvolved tissue, although
this technique is often limited by proximity to functional organs. For many tumors, particularly those in which clear margins cannot be obtained, radiation therapy is utilized as an adjunctive treatment. Radiation therapy may be helpful as an adjuvant treatment in certain settings. Effective RT employs a radiation field that includes the tumor site and at least 5 cm of peripheral tissue, with doses ranging from 50 to 65 Gy. However, the overall impact of RT on local recurrence and survival is far from clear. Although further research is needed to better define the role of RT, current NCCN guidelines state that adjuvant therapy should be considered on an individual case basis [5,6,14,15].

The chemotherapy is also considered in the treatment of PRS. Doxorubicin with or without ifosfamide had long been considered by many to be first-line therapy, but gemcitabine and docetaxel have also shown promising in vivo and in vitro synergism for sarcomas of various histologies [3].

Recent insights into the molecular features of MFH have enabled early clinical trials to explore the potential use of biologic agents in the treatment of advanced disease, providing an exciting avenue for future research. Although promising, widespread use of molecular-targeted therapy for MFH appears years away [6,16].

Post-irradiation sarcomas of bone and soft tissue are a high-grade lesion with worse prognosis, frequent local recurrence and distant metastases. The overall reported 5-year survival rates for patients with PRS are poor and ranges from 8.7 to 22% in different studies [5].

To summarize, the long-term survival of patients subjected to RT is linked with the risk to develop second cancer; hence, patient follow up and a high index of suspicion are crucial. PRS must be considered in patients treated with RT when a soft tissue mass is seen in the previously irradiated area and it should be differentiated from metastasis of primary tumor with the help of appropriate markers as it has a grim prognosis [5].

References
13. NCCN_guidelines.pdf [Internet]. [cited 2012 Dec 9].
15. Phase I Study of Ipilimumab (Anti-CTLA-4) in Children and Adolescents With Treatment-Resistant Cancer - Full Text View - ClinicalTrials.gov [Internet]. [cited 2012 Dec 9].
16. Phase II Study of Sunitinib Malate for Metastatic and/or Surgically Unresectable Soft Tissue Sarcoma - Full Text View - ClinicalTrials.gov [Internet]. [cited 2012 Dec 9].