

Myxofibrosarcoma Following Chemotherapy and Radiotherapy for Hodgkin's Lymphoma: Case Study and Review

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Abstract

Introduction: Although radiation-induced sarcomas are widely documented, most reports focus on pleomorphic malignant fibrous histiocytomas (high-grade undifferentiated pleomorphic sarcomas); few case studies involve myxofibrosarcomas. This paper reports on a grade II myxofibrosarcoma of the neck arising secondary to earlier chemotherapy and radiotherapy.

Material and methods: A 61-year-old male received chemotherapy plus radiotherapy in 1983 for nodular sclerosing Hodgkin's lymphoma. Twenty-six years after completing treatment, the patient developed a grade II myxofibrosarcoma involving radiated soft tissue on the left side of the neck.

Results: The tumor was removed. The tumor mass weighed 90 g and measured 6 × 5 × 4.5 cm and the histological examination revealed a grade-II superficial malignant myxoid spindle-cell tumor displaying a multinodular growth pattern. Immunohistochemical staining was positive for CD34 and negative for smooth muscle actin and desmin.

Conclusions: Given the increasing use of adjuvant therapies, particularly in the early stages of cancer, patients should be closely monitored to ensure detection of radiation/chemotherapy-induced sarcomas.

Keywords: Hodgkin's lymphoma; Post-radiotherapy; Post-chemotherapy; Myxofibrosarcoma; Postradiotherapy sarcoma; Tumor

Introduction

Radiotherapy (RT) has become a basic tool in cancer treatment; the vast majority of cancer patients receive RT at some point in the course of their disease. The development of radiation-induced sarcoma during treatment is rare (0.035%-0.8%) [1,2]. The incidence of head and neck carcinomas and sarcomas is around 0.70% (3-5). Most published reports deal with secondary tumors following treatment for breast cancer, lymphoma and cancer of the genitourinary system [2,4,6-8]. The most common histological subtypes are pleomorphic malignant fibrous histiocytoma (high-grade undifferentiated pleomorphic sarcoma), osteosarcoma, fibrosarcoma, angio-lymphosarcoma and a number of poorly-defined lesions grouped under the generic heading spindle-cell sarcoma [1-6,9].

A review of the literature reveals only three reports of malignant fibrous histiocytoma following radiation therapy and chemotherapy for Hodgkin's lymphoma [2,9-13]; its incidence is therefore not clearly established. The authors report on a medium-grade soft-tissue myxofibrosarcoma (myxoid malignant fibrous histiocytoma) in a patient who had received radiotherapy and chemotherapy twenty-six years earlier for nodular sclerosing Hodgkin's lymphoma.

Case Report

A 61-year-old man consulted the cancer unit because of a lesion on the left side of the neck, of six weeks' standing. Patient history included

a nodular sclerosing Hodgkin's lymphoma in the mediastinum, diagnosed 26 years earlier and treated with mantle radiotherapy and neck irradiation (45 Gy) plus 8 cycles of chemotherapy (C-MOPP).

CT scan revealed a lesion in the left paravertebral muscle region, with loss of fat plane and a focal heterogeneous increase in contrast uptake. Neither the paravertebral muscles nor the sternocleidomastoid muscle were affected. Maximum width on cross sections was 3.3 × 5 cm, and maximum craniocaudal length was 5.5 cm. (Figure 1).

Fine-needle aspiration biopsy (FNAB) revealed two clearly-defined cell populations (spindle cells and occasionally-binuclear polygonal cells) embedded in a myxoid matrix with collagenized stromal tissue (Figure 2). The diagnosis was sarcoma consistent with myxofibrosarcoma; the tumor was removed and referred for histological examination. The tumor mass weighed 90 g and measured 6 × 5 × 4.5 cm. At gross examination, the tumor surface was uneven, containing yellowish fatty areas and brownish elastic areas of muscle tissue. The cut surface displayed a well-defined nodular formation of maximum size 4 cm, with a central, heterogeneous nodular area measuring 3 cm, containing soft areas of mucoid appearance. Perinodular tissue was whitish-gray and gelatinous (Figure 3). Histological examination revealed a hypocellular myxoid tumor displaying a multinodular growth pattern, curvilinear capillaries and peripheral tumor-cell condensation. Cells were spindle-shaped or stellate, with hyperchromatic nuclei. In addition to these myxoid areas, which accounted for >50% of the lesion, other more compact areas comprised spindle-cells and polygonal cells arranged in bundles and whorls. Nuclear pleomorphism and multinucleate cells were common in these areas. The mitotic index was 5-6/10HPF. Areas of

necrosis, though extensive, accounted for <50% of the lesion (Figures 4 and 5). The tumor extended to the surgical margin over 15% of its perimeter. Immunohistochemical analysis revealed diffuse positive staining for CD34 and focal positive staining for smooth muscle actin; staining was negative for desmin, CD31 and S-100 protein. The proliferation index (Ki-67 expression) in hypercellular areas was 10-15%. The tumor was diagnosed as a grade II myxofibrosarcoma (myxoid malignant fibrous histiocytoma).

The patient underwent adjuvant external radiotherapy to the surgical bed (55 Gy) and at the last check-up, 13 months later, showed no signs of local recurrence or metastasis.



Figure 1: Computed tomography image of the neck showing a laterocervical mass with a soft tissue density.

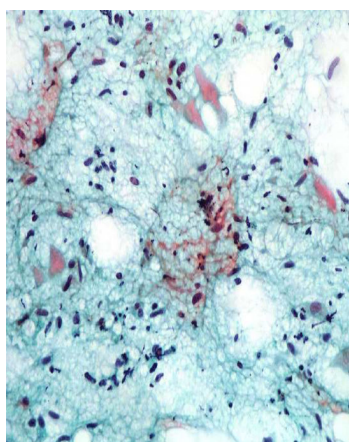


Figure 2: Fine-needle aspiration biopsy showing bland spindle cells in a background of myxoid matrix. Papanicolaou stain, X 20.

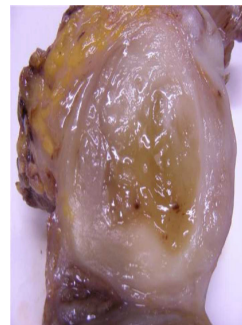


Figure 3: Gross appearance of the myxofibrosarcoma.

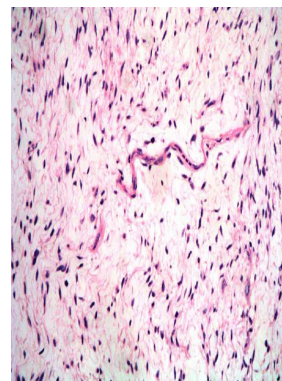


Figure 4: Histologic section showing whirled fibroblastic cells in a myxoid background with prominent capillaries. HEX20.

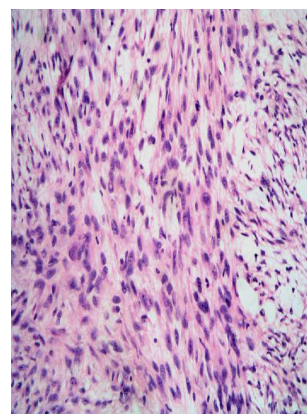


Figure 5: Solid sheets of atypical and spindled cells with abundant eosinophilic cytoplasm. There is often a remarkable but characteristic sharp transition between hypo- and hypercellular areas. HE X40.

Discussion

In the 1960s, radiotherapy alone was the standard treatment for early-stage Hodgkin's lymphoma (HL). In the 70s and 80s, however, it

became apparent that HL patients treated with radiotherapy were at greater risk of developing secondary malignancies than the general population [10,11]. From the 1990s onwards, therefore, it was recommended that patients with early-stage HL should receive induction chemotherapy followed by radiotherapy. However, secondary malignancies have also been reported in HL patients undergoing this combined treatment (chemotherapy with alkylating agents, radiotherapy to both sides of the diaphragm, and relatively high radiotherapy doses in this setting), although the incidence is lower than in patients receiving radiotherapy alone [10].

Secondary malignancies in HL patients have traditionally been divided into three major categories: leukemias, non-Hodgkin's lymphomas (NHL) and solid tumors. The risk of leukemia is linked to chemotherapy and alkylating agents, and is dose-dependent. The increased risk of NHL may be related to treatment-induced immune suppression (radiotherapy/chemotherapy) or may be part of the natural history of HL, and especially of lymphocyte-predominant HL [12]. At present, due to the prolonged survival of HL patients, solid tumors have become the major subtype of secondary malignancy. They typically develop >10 years after the initial treatment [12,13], and the risk persists for over 30 years. The current risk (\pm standard deviation) of developing a secondary malignancy after 15 years (with the exception of basal cell carcinoma) in radiation-treated HL patients is 9.9% (\pm 2.8), compared with 1.8% (\pm 1.8) for patients treated with chemotherapy, whilst the risk in patients undergoing combined chemotherapy/radiotherapy is 12.9% (\pm 2.9%) [13].

The diagnosis of radiation-induced sarcoma is based on the following criteria, set out by Cahan in 1948: a) prior history of radiation exposure and existence of a latency period; b) occurrence of the sarcoma in or near the field of radiation; and c) histological confirmation of a sarcoma that is different from the primary cancer [1].

The length of time required between radiation exposure and sarcoma formation is one of the most widely-debated criteria: some authors suggest a minimum latency period as short as one month, [1,5], although most tend to think in terms of several years [1-6,9,10,12,13].

A review of the literature reveals only three reports of malignant fibrous histiocytoma following radiation therapy and chemotherapy for Hodgkin's lymphoma (Table 1). Saggia et al. [13,14] reported a high-grade pleural sarcoma following a latency period of 15 years, while Nonaka et al. [9] noted a case of inflammatory malignant fibrous histiocytoma of the anterior chest wall 18 years after the patient received radiotherapy alone. Mandal et al. [2] reported on a patient with a history of tumor recurrence, treated with chemotherapy and radiotherapy, who developed a malignant fibrous histiocytoma of the knee 21 years after treatment was started. In the present case, a grade II myxofibroma was found in a patient treated for HL 26 years earlier, with radiotherapy and chemotherapy. In all four cases, the radiation dose varied between 40 and 45 Gy, and the latency period ranged from 15 and 26 years.

Author	Saggia et al [14]	Nonaka et al [10]	Mandal et al [2]	Present case 2010
Age/Sex	51/M	59/F	42/F	61/M
Diagnosis	High-grade pleural sarcoma	Inflammatory MFH	MFH	Grade II myxofibrosarcoma (myxoid MFH)
IHC profile	CD34 (+) CK, EMA, Calretinin and S-100 (-)	Vimentin (+) SMA, Desmin, S-100, EMA, CK and CD45 (-)	CD68 and vimentin (+) SMA, S-100 and desmin (-)	CD34 (+) and focal SMA (+). Desmin, myoglobin, CD-31 and S-100 (-)
Location	Pleura	Chest wall	Right knee	Left side of neck
HL	Stage IIIA	(No data)	Lymphocyte-depletion HL (Inguinal) Stage III	Nodular sclerosing HL (mediastinum) Stage II
HL Treatment: Radiotherapy (RT)/ Chemotherapy (CT)	RT: 40Gy + CT: MOPP (3 cycles)	RT to neck (54Gy), mediastinum (41Gy) and para-aortic region (40Gy)	-MOPP (4 cycles) -MOPP (6 cycles). -RT right tibia (44Gy) -RT right humerus (44Gy) +CT (6 cycles ABVD)	Mantle RT with neck irradiation (45Gy) + CT: C-MOPP (8 cycles)
Latency Period (YEARS)	15	18	21	26
Sarcoma Treatment	CT (Iphosphamide and epirubicin)	Surgical excision	Patient abandoned	Surgical excision + RT (55Gy)
Evolution	Death at 5 months	Death at 64 days	Unknown	No metastasis or local recurrence.

Table 1: Malignant fibrous histiocytomas following radiotherapy/chemotherapy for Hodgkin's Lymphoma.

Generally speaking, the prognosis for radiation-induced sarcomas is worse than that of other sarcomas at a similar stage, because they tend

to be radiation-resistant. However, a favorable response to radiotherapy is reported in many cases, as here. The effects of

chemotherapy are equally controversial [2,4,9]. Given the likelihood of local recurrence and remote metastasis, prolonged close monitoring of these patients is essential to ensure early detection and enable full surgical removal of the tumor.

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