Unusual presentation of more common disease/injury

High-grade myxofibrosarcoma presenting at the spermatic cord after radiotherapy for prostate cancer

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Summary

A 72-year-old man with a history of prostate cancer presented 7 years postradiotherapy with a painless, egg-sized, rapidly growing nodule on the left groin at the radiation site. He underwent left high orchiectomy under a diagnosis of groin lymph node metastasis of prostate cancer. The tumour had penetrated deep into the internal inguinal ring and was resected as proximally as possible to the internal ring with a positive surgical margin. Macroscopically, the left testis was intact in the resected specimen. Immunohistochemical staining revealed that the tumour consisted of myxofibrosarcoma (MFS) with spindle cells; and was positive for vimentin, cytokeratin (AE1/AE3), MIB-1 and CD68, and negative for α -SMA, S-100, CD34 and myogenin. Thus, the tumour was diagnosed as high-grade MFS of the spermatic cord. Postoperative CT revealed a right renal tumour and adrenal tumour. Right radical nephrectomy was performed and the patient was doing well at 10-month follow-up.

BACKGROUND

Myxofibrosarcoma (MFS) is a common soft-tissue sarcoma in older adults¹ that can arise de novo or be induced by radiation. MFS has previously been referred to as myxoid malignant fibrous histiocytoma (MFH) and now encompasses a spectrum of myxoid tumours with similar characteristics to MFH.¹ The distinction between MFS and MFH is still unclear, and the term MSF is often used interchangeably with the myxoid variant of MFH.^{1–3}

Radiation-induced sarcoma implies that radiation is the sole aetiological factor, but carcinogenic agents or as yet unknown factors may also contribute to the aetiology. The first clinical association between exposure to radiotherapy and sarcoma was recognised in 1992 by Beck,⁴ in a description of bone sarcomas in patients who had received radiotherapy for tuberculous arthritis. Thereafter, the number of patients with bone or soft-tissue sarcoma has increased following treatment with radiation for malignant diseases.^{5–6} These tumours usually occur many years after exposure to radiation and are associated with a poor prognosis.^{6–8}

Earlier literature characterises postradiation bone sarcomas much better than their soft-tissue counterparts because of their more common occurrence in the era of orthovoltage radiotherapy, since this frequency is absorbed more quickly by bone than by soft tissues.⁹ A wide range of therapeutic doses (8 to >60 Gy) have been reported to result in a postradiation sarcoma⁹; the majority of cases received a median of about 50 Gy.^{9–10} In a review of secondary malignancies after Ewing's sarcoma, Kuttish *et al* found no secondary sarcomas in patients receiving <48 Gy, compared to an absolute risk of 130 cases per 10 000 person-years of observation among patients who had received ≥ 60 Gy, suggesting dose dependence.^{9–12}

Herein, we describe a case of high-grade MFS in the spermatic cord after 7 years of latency. In this case,

diagnosis of radiation-induced sarcoma was based on the long-term disease-free period, location of the mass at the periphery of the radiation field and aggressive imaging appearance. MFS with a spermatic cord origin is very rare, with no previous case reports of development 7 years after radiotherapy.

CASE PRESENTATION

The patient was a 72-year-old man with a history of radiation therapy for prostate cancer. He had been diagnosed with moderately differentiated adenocarcinoma with a Gleason score of 3+3 using needle biopsy of the prostate in 1997. First, he underwent maximum androgen blockade for 6 years, without reduction in his prostate-specific antigen level. Therefore, radiation therapy at 74 Gy was performed as the secondary therapy. Seven years later, he presented with a small hen egg-sized nodule penetrating deep into the left groin, adjacent to and within the prior radiation site.

TREATMENT

Left high orchiectomy was performed under a diagnosis of groin lymph node metastasis of prostate cancer. The tumour had penetrated deep into the internal inguinal ring and was resected as proximally as possible to the internal ring with a positive surgical margin (figure 1).

OUTCOME AND FOLLOW-UP

Microscopic examination revealed a tumour consisting of myxoid stroma (MFS) with spindle cells, with a large variation in histological findings. Immunohistochemical staining was positive for vimentin, cytokeratin (AE1/AE3), MIB-1 and CD68 and negative for α -smooth muscle actin, S-100, CD34 and myogenin (figures 2 and 3). Thus, the tumour was diagnosed as high-grade MFS of the spermatic cord.

Figure 1 (A) Extraction specimen, the tumor shows nodular growth. The testis is grossly intact (arrow). (B) The cut surface of the specimen, tumor growth fibrous septa. (size about 3×3 cm).

A postoperative CT scan revealed a right renal tumour and adrenal tumour, but no involvement of retroperitoneal lymph nodes. Thus, right radical nephrectomy was performed. On histopathological examination, clear cell carcinoma with grade G2>G3 (Fuhrman grade 3, size 4.5×3.0 cm, pT1b, INF-ALFA, V1, LY 0, EG, FC 0, IM 0, RC-INF 0, RP-INF 0, S-INF 0) was diagnosed; and the adrenal tumour was diagnosed as lipoma (size: 1×1 cm) (figure 4). At 10-month follow-up, the patient was doing well with an uneventful postoperative clinical course.

DISCUSSION

MFS is a common soft-tissue sarcoma in older adults. Pleomorphic undifferentiated sarcoma is currently used to describe lesions previously classified as high-grade MFH.¹³ Indeed, resolution of these cases is necessary as the degree of myxoid change may be inversely correlated with the risk of metastasis.¹⁴ Approximately two-thirds of cases present in the skin, typically involving dermal or subcuta-

neous tissue of the lower extremities, although presentation involving the upper extremity or trunk has also been seen.¹⁵

Weiss has attempted to distinguish MSF from MFH.¹⁴ Misdiagnosis of sarcomas has arisen because the superficial portion of MSF often appears benign, despite evidence of malignancy in deeper tissue regions.^{16 17} Since MFH is currently diagnosed as a sensitive soft-tissue sarcoma, its classification follows the 2004 WHO classification. Histopathologically, MFS presents with a broad spectrum of cellularity, pleomorphism and proliferative activity.¹⁵ On immunohistochemical analysis, MFS stains strongly for vimentin and may focally express muscle-specific actin.¹² Various staining techniques have proven to be useful in its diagnosis. For example, Alcian blue staining at varying pHs can help delineate MFS from tumours containing sulphated glucosaminoglycans, such as myxoid chondrosarcoma.¹⁸ In the present case, expression of vimentin, cytokeratin (AE1/AE3), MIB-1 and CD68 was found.

Figure 2 (A–D) The tumour was composed of spindle cells with mild to moderate atypia, with some cells showing a few mitotic figures. The tumour contained myxoid or focally collagenous stroma.

Figure 3 (A–D) Immunohistochemical staining was positive for vimentin, cytokeratin (AE1/AE3), MIB-1 and CD68, (E–H) Negative for α -smooth muscle actin, S-100, CD34 and myogenin.

Since MFS is an unencapsulated entity capable of infiltrating along the facial planes and between muscle fibres, it represents a locally aggressive sarcoma that is difficult to eradicate. Zagars *et al*¹⁹ found that de novo lesions without previous irradiation, lesions <10 cm in diameter, and negative resection margins were predictors of a good survival outcome, and suggested that the presence of metastatic diseases, complete resection in patients with a localised disease, and the size of the primary tumour in

patients who underwent complete resection were of prognostic significance. However, survival was independent of histological subtype or site of disease.¹⁹

Tumour size and grade are the two most important prognostic factors for soft-tissue sarcomas, including those associated with radiation therapy. The therapy is therefore dictated by the risk of distant metastases.²⁰ High-grade sarcomas >5 cm should be treated with primary chemotherapy followed by a margin-negative

right renal tumor (arrow)
clear cell carcinoma with grade G2>G3 (Fuhrman classification of grade 3, with a size of 4.5 x 3.0 cm, pT1b, INF-ALFA, V1, LY 0, EG, FC 0, IM 0, RC-INF 0, RP-INF 0, S-INF 0

right adrenal tumor
lipoma(size: 1 x 1 cm)

Figure 4 Resected specimen (laparoscopic radical nephrectomy).

surgical excision of the residual disease. All low-grade tumours and high-grade tumours ≤ 5 cm should be treated with a margin-negative surgical excision, and systemic chemotherapy should be considered when a negative margin is difficult to accomplish.²¹

The local recurrence and metastatic rates of MFS are 31–80% and 14–23%, respectively.^{14 15 19 20} Regional metastatic recurrence of new nodules of high-grade MFS manifest as a low-grade recurrence or a new, radiation-induced soft-tissue sarcoma.¹² However, radiotherapy is an unlikely cause of recurrence.¹² The majority of radiotherapy cases report median therapeutic doses of 50–60 Gy.^{9 11 12} Zhu *et al*¹⁰ reported that a total dose of 60 Gy (2 Gy daily doses for 3–5 days per week) administered to the bronchial stump, bilateral hilum, mediastinum and ipsilateral supraclavicular fossa resulted in no immediate complications and no signs of recurrence on chest x-ray at 8-year follow-up. Dua *et al*²¹ described a rare case of recurrence of treated cervical cancer confined to the para-aortic nodal group after a disease-free interval of 13 years. However, data on the grade of these tumours are limited. In the Memorial Sloan Kettering Cancer Center (MSKCC) series, 87% of the tumours were high grade.¹¹ Most patients presented with a locally advanced tumour that was typically >5 cm in size and deep in the investing fascia. In the MSKCC series, survival was independent of the site of disease, bone versus soft tissue origin, histology and latency period.²²

Spermatic cord tumours are relatively rare, with 30–50% being malignant and most being soft-tissue sarcomas.^{11 12} Of 47 reported cases of spermatic cord sarcoma, 51% were liposarcoma, 19% leiomyosarcoma, 13% rhabdomyosarcoma and 5% MFS.¹² The reported mean age for such sarcomas is 58 years.²³ A recent review of 175 patients with a history of sarcoma used the following criteria to identify radiation-induced osteosarcoma: (1) osteosarcoma arose within a previously irradiated field; (2) the new sarcoma was histologically distinct from the original neoplasm; (3) the new sarcoma was not evident at the time of radiation and (4) a distinct latency period was apparent.⁹ According to these criteria, 9% of the cases were radiation-induced osteosarcoma, with an average age of 35 year and a median latency period of 12.5 years. Of the 14 patients treated surgically, 86% developed local recurrence; the median survival period was 29 months and the 5-year survival rate was 29.6%.⁹

Radiation-induced MFS is still uncommon, but may increase in incidence as use of radiotherapy become more common. MFS is locally aggressive and has a high rate of local recurrence and mortality, despite aggressive surgical, hormonal and medical management.⁹ Moreover, recurrence may develop many years after exposure to radiation and is associated with a poor prognosis.²¹ Thus, careful observation is warranted to prevent radiation-associated MFS. The case reported here was our first experience of radiation-induced MFS, even though radiotherapy is common practice for prostate cancer at our hospital. We could not confirm radiotherapy as the cause of the new lesion, but recurrence is unlikely after a 7-year latency period. Adequate therapy for radiation-induced MFS has not been established and patients are at significant risk for metastasis. Development of effective adjuvant treatment is thus warranted. In the future, radiotherapy combined with surgery may be the standard treatment, and counseling prior to radiotherapy should include discussion of the risks for soft-tissue sarcoma due to its high local recurrence and metastatic rates.

Learning points

- Radiation-associated myxofibrosarcoma (MFS) may occur after a long period following radiotherapy.
- MFS may be positive for vimentin, cytokeratin (AE1/AE3), MIB-1 and CD68, and negative for α -SMA, S-100, CD34 and myogenin.
- There is a significant risk of metastasis of MFS and effective adjuvant therapy is required.

Competing interests None.

Patient consent Obtained.

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