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Case report

'Radiation-induced pleomorphic sarcoma with rhabdomyoblastic differentiation of the lower limb following treatment of vaginal squamous cell carcinoma – A case report and review of the literature'

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ABSTRACT

We present the case of a 59-year-old woman who developed a right thigh pleomorphic sarcoma with rhabdomyoblastic differentiation 6 years following radiotherapy for a vaginal squamous cell carcinoma. The overall 5-year survival for a gynaecological malignancy is more than 80 % and as overall cancer survivorship and life expectancy improves, the incidence of radiation-induced malignancy is increasing (Bjerkehagen et al., 2013). As the prognosis of those malignancies is usually poor, clinicians must have a high index of suspicion to try to detect these cases early.

1. Introduction

Radiation-induced malignancies (RIM) are a well-known but rare complication of radiotherapy. The incidence appears to be increasing as cancer survivor rates improve (Bjerkehagen et al., 2013). RIM have a poor prognosis and thus, early diagnosis is important. We present the case of a 59-year-old woman with a pleomorphic sarcoma with rhabdomyoblastic differentiation of the anterior thigh following radiation for a vaginal squamous cell carcinoma with a 6-year latency period.

2. Case report

A 59 year-old woman presented to her General Practitioner with worsening right lower limb oedema, right hip and lateral knee pain and a new 'stooped' gait. Seven years prior, she had been treated for a FIGO stage II moderate-to-poorly differentiated vaginal squamous cell carcinoma with primary chemo-radiotherapy. Her radiotherapy involved external beam treatment with Intensity Modulated Radiation Therapy (IMRT) to the vagina and inguinal and pelvic nodes bilaterally with 61.87 Gy in 29 fractions (Fig. 1). She also received concurrent weekly cisplatin (40 mg/m^2) for 6 weeks. She completed her treatment without interruption and on follow-up she was noted to have complete metabolic response of her vaginal carcinoma on PET scan.

After 6 years, she presented to her GP with progressive lower limb pain, and limb odema and a lump in her right proximal thigh. Imaging studies including an MRI scan showed a 17 × 8.6 × 7.5 cm moderately defined heterogenous region in the right vastus intermedius muscle and a 6.7 × 4.4 × 4.3 cm soft tissue mass in the vastus medialis muscle not involving femur but abutting neurovascular bundle, suggestive of a sarcoma (Fig. 2).

An ultrasound-guided biopsy of the mass showed a Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLLCC) grade 3 pleomorphic sarcoma with rhabdomyoblastic differentiation characterised by polygonal cells with voluminous eosinophilic cytoplasm and variable staining with SMA, desmin and MyoD1. FISH did not show MDM2 amplification, excluding a dedifferentiated liposarcoma. Staging PET scan showed no evidence of nodal or distant metastases.

This case was discussed at the Sarcoma Multi-Disciplinary Team (MDT) meeting which concluded that this was likely to be a a radiotherapy-induced soft-tissue sarcoma of the proximal right lower limb with occlusion of right femoral neurovascular bundle. The treatment recommendation was surgery followed by adjuvant chemotherapy. Pre-operative radiation was not recommended due to previous radiation to this site. The patient proceeded to surgery and a right hip disarticulation was performed, revealing a well demarcated intramuscular tumour adherent to the femur measuring 130 × 100 × 80 mm with

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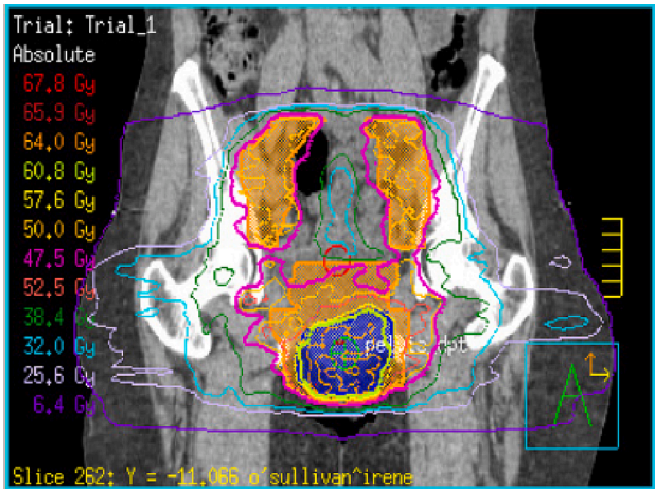

Fig. 1. Radiation treatment with IMRT to the vagina, and inguinal pelvic lymph nodes bilaterally with 61.87 Gy in 29 fractions.

a heterogenous cut surface including solid fleshy tumour, haemorrhage, cystic degeneration and necrosis.

Microscopically the tumour showed a highly pleomorphic population of cell with solid and fascicular architecture (Fig. 3a). Necrosis was confirmed and there was brisk mitotic activity including atypical mitotic figures (Fig. 3b) with up to 21 mitoses per 10 high power fields. Rhabdomyoblastic differentiation was observed with both spindled and rounded rhabdomyoblasts with abundant voluminous eosinophilic cytoplasm (Fig. 3c) showing extensive reactivity for SMA and desmin (Fig. 3d). The tumour was seen to invade the femur cortical bone and marrow space focally. Perineural invasion was identified. The margins were clear.

The Sarcoma MDT confirmed tumour was likely to be a Radiation Induced Sarcoma (RIS) given her history of radiotherapy at this site and the latency period of 6 years. The patient received additional adjuvant ifosfamide and doxorubicin chemotherapy.

18 months after the resection of the RIS, she had a wide local excision of a loco-regional metastasis. She currently is in remission 8 years after her radiotherapy.

3. Discussion

There are various definitions of RIS which generally have to fulfill the following criteria (Cahan et al., 1998, Bjerkehagen et al., 2008).

(1) The resulting sarcoma has developed within a prior radiation field (in the area encompassed by 5 % isodose line)
(2) A latency period of at least 2 years since the radiotherapy
(3) The sarcoma must be histologically distinct from the index tumour

The majority of RIS following treatment for a gynaecological malignancy have been identified as undifferentiated pleomorphic sarcomas or angiosarcomas (Gladdy et al., 2010). The original pathology of this case showed marked rhabdomyoblastic differentiation. Rhabdomyosarcomas are a particularly rare histological subtype of RIS that originate from myogenic progenitor cells and contribute to less than 3 % of all RIS overall (Cha et al., 2004).

RIS constitutes 2.5–5.5 % of all sarcomas, the majority of which occur after treatment for lymphomas, breast, head and neck ~~as~~ well as gynaecological malignancies (Bjerkehagen et al., 2008). In women undergoing primary radiotherapy for a gynaecological malignancy, the absolute risk of a post-radiation sarcoma is estimated to be between 0.03 and 0.8 % with a 0.03–0.8 % 10 year cumulative risk (Mark et al., 1996, Bjerkehagen et al., 2008).

The development of RIS may be influenced by factors such as radiotherapy dose, age at initial exposure, radiation technique and genetic tendency. As radiation carcinogenesis is a stochastic late effect, there is no 'safe' or threshold dose below which RIS are not seen. RIS have occurred at doses less than 15 Gy (Samartzis et al., 2013). However, the risk of RIS does appear to rise with increasing radiation dose but there is uncertainty about the shape of the dose–response curve at high doses (Rubino et al., 2005). RIS is generally thought to occur at doses that induce sublethal damage in normal tissues resulting in mutagenic responses and disorganized reparative proliferation and ultimately, tumour induction.

It has been postulated that the use of newer radiation techniques such as IMRT may result in an increase in RIM. There are two proposed reasons for this, including that IMRT involves the use of more fields compared to three-dimensional conformal radiation therapy and thus the integral dose to the patient is higher, i.e., a larger volume of normal tissue is exposed to lower doses of radiation. Secondly, delivery of a specified dose to the isocenter from a modulated field via IMRT will require the linear accelerator to be energized for longer (i.e., more monitor units are needed) compared with delivering the same dose from an unmodulated field. This then leads to a higher total body dose due to leakage radiation (Hall, 2006). More robust data needs to be acquired to

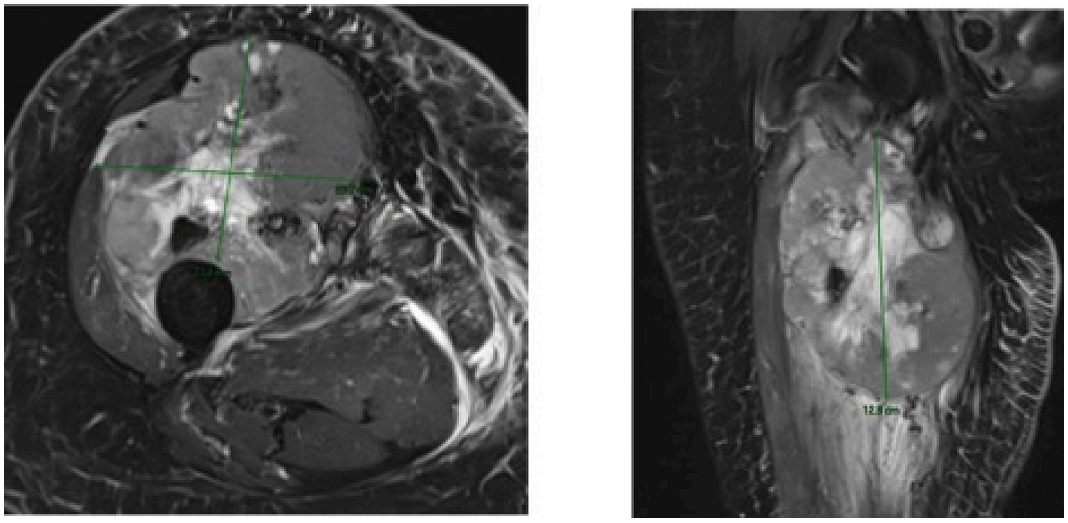

Fig. 2. MRI: Transverse and coronal image of right anterior compartment thigh mass.

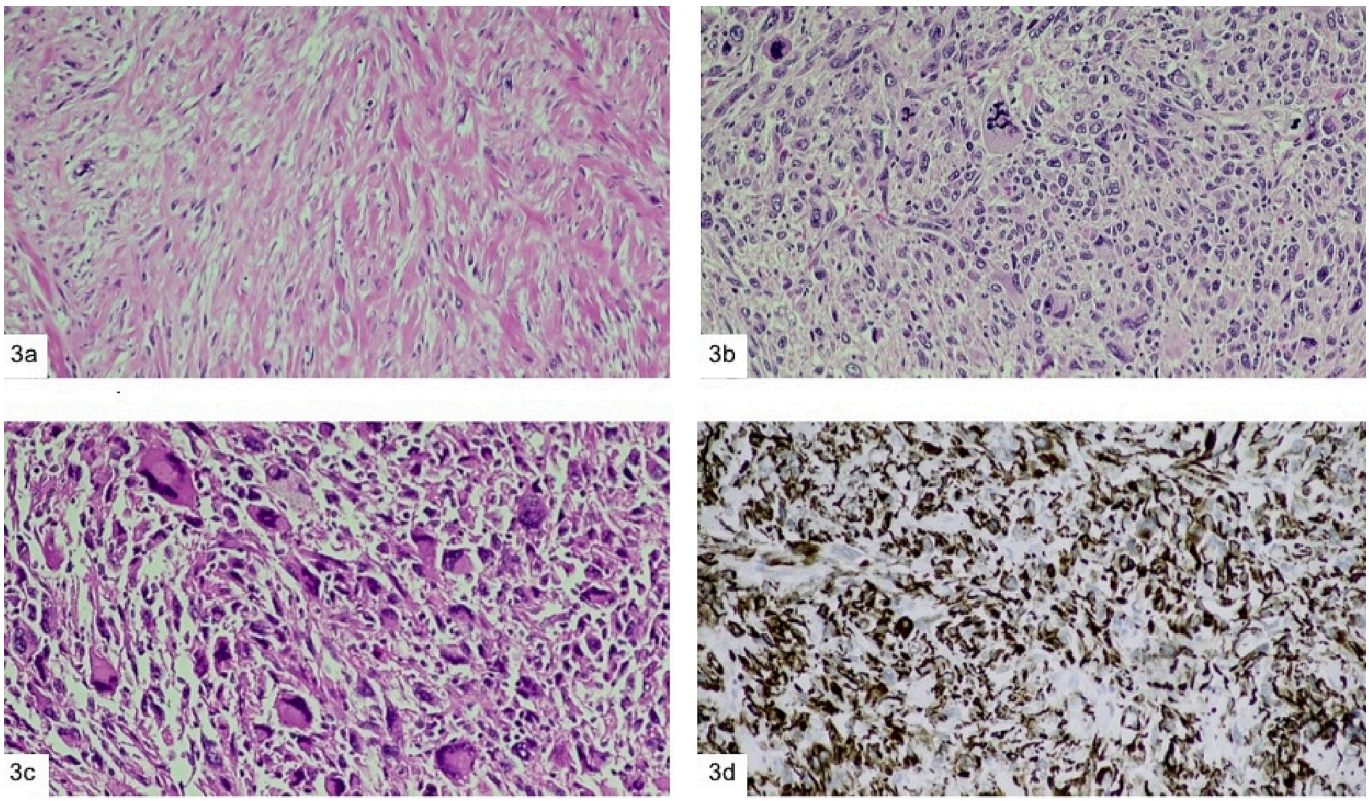

Fig. 3. a: Microscopy at 20X shows atypical spindle cells and spindled rhabdomyoblasts with fascicular architecture. b: Microscopy at 20X shows a pleomorphic tumour consisting of epithelioid, spindled and bizarre multinucleate cells with brisk mitotic activity including atypical forms. c: Microscopy at 20X shows an admixture of spindled and rounded rhabdomyoblasts. d: Diffuse desmin positivity by immunohistochemistry.

confirm these theories.

The prognosis for stage-matched RIS is poor compared to sporadic high-grade soft-tissue sarcomas. Recurrence free survival is 1.7-fold worse for a RIS compared with a sporadic soft-tissue sarcoma (Gladdy et al., 2010). A retrospective case series of 43 patients with radiation-induced rhabdomyosarcoma specifically demonstrated only a 42 % 3 year overall survival (Dang et al., 2013). A case control study comparing 98 RIS to 239 sporadic high-grade sarcomas showed 5 year survival of only 32 % for RIS compared to 51 % for sporadic sarcomas (Bjerkehagen et al., 2012).

The poor prognosis of RIS patients is not due to the previous radiotherapy per se but related to other factors including; difficult and thus a delayed diagnosis of a tumour in previously radiated tissue, compromised resection margins due to the proximity of the tumour to critical structures, limited treatment options in a maximally radiated field including the technical difficulty of operating within an irradiated area, difficulties with re-irradiation when surrounding normal tissues have been treated to near tolerance, poor tumour sensitivity to chemotherapy, the high-grade nature of the vast majority of RIS and host immunosuppression resulting from tumour-related factors and previous treatment (Bjerkehagen et al., 2012; Murray et al., 1999; & Cha et al., 2004).

Treatment of RIS may include surgical resection, radiotherapy and chemotherapy. RIS are commonly radiation resistant and chemotherapy is ineffective due to treatment resistance and surrounding fibrosis and thus the mainstay of treatment is surgical excision. However, RIS are often advanced at the time of diagnosis and thus inoperable. Even when operable, due to fibrosis and obliteration of tissue planes, obtaining adequate surgical margins can be challenging with one series reporting an R0 resection rate of only 54 % which is prognostic factor for increased risk of local recurrence (Cha et al., 2004).

The extent of rhabdomyoblastic differentiation seen in the original resection of this tumour led us to look into the literature for reported cases of radiation-induced rhabdomyosarcomas arising in women treated with radiotherapy for gynaecological malignancies. Mindell et al. (1997) reported on a 49-year-old female who received adjuvant radiotherapy for cervical cancer and 4 years later was diagnosed with a pelvic rhabdomyosarcoma. She passed away 18 months later. Almohsen et al. (2021) reported on a 48-year-old woman treated with chemo-radiotherapy for cervical squamous cell carcinoma who developed rhabdomyosarcoma of the vulva, vagina, perineum, distal rectum, proximal anal canal and posterior bladder with involvement of the gluteal muscles. She was treated with chemotherapy and radiation but passed away shortly after diagnosis. Lee et al. (1990) reported on a 70-year-old female who had radiotherapy for cervical squamous cell carcinoma and developed a rhabdomyosarcoma of the uterus which was treated surgically. Her outcome after post-operative discharge was not reported.

In conclusion, we present a case of a RIS following primary radiation therapy for vaginal carcinoma. The phenomenon of RIS is rare but increasing in incidence. The most common subtypes of RIS are undifferentiated pleomorphic sarcomas, angiosarcomas and osteosarcomas but divergent differentiation can occur and other rare subtypes should also be included in the differential diagnosis. It is important for GPs and Gynaecological-Oncology teams to have a high index of suspicion in anyone presenting with a pathology in a previous radiation field and thoroughly evaluate for a RIS. If diagnosed early, surgical excision with negative margins may offer best chance of long-term survival.

CRediT authorship contribution statement

Anna Nicholson: Conceptualization, Writing – original draft, Writing – review & editing, Project administration. **Martin Oehler:** Conceptualization, Writing – review & editing, Supervision. **Alexandra**

Jolley: Writing – review & editing. **Ragu Gowda:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Almohsen, S.S., Alnuaim, H., Salim, A.A., Arabi, H., 2021. Pelvic Radiation-Induced Sarcoma with Rhabdomyoblastic Differentation Following Treament of Cervical Cancer. Cureus 13 (6), e15428.

Bjerkehagen, B., Smeland, S., Walberg, L., Skjeldal, S., Hall, K.S., Nesland, J.M., Småstuen, M.C., Fosså, S.D., Saeter, G., 2008. Radiation-induced sarcoma: 25-year experience from the Norwegian Radium Hospital. Acta Oncol. 47 (8), 1475–1482. https://doi.org/10.1080/02841860802047387.

Bjerkehagen, B., Småstuen, M., Hall, K., et al., 2012. Why do patients with radiation-induced sarcomas have a poor sarcoma-related survival? Br. J. Cancer 106, 297–306.

Bjerkehagen, B., Smastuen, M.C., Hall, K.S., Skjeldal, S., Bruland, O.S., Smeland, S., et al., 2013. Incidence and mortality of second sarcomas – A population-based study. Eur. J. Cancer 49, 3292–3302. https://doi.org/10.1016/j.ejca.2013.05.017.

Cahan, W.G., Woodard, H.Q., Higinbotham, N.L., Stewart, F.W., Coley, B.L., 1998. Sarcoma arising in irradiated bone: report of eleven cases. 1948. Cancer 82, 8–34.

Cha, C., Antonescu, C.R., Quan, M.L., Maru, S., Brennan, M.F., 2004. Long-term results with resection of radiation-induced soft tissue sarcomas. Ann. Surg. 239(6):90, 3–10. https://doi.org/10.1097/01.sla.0000128686.51815.8b.

Dang, N.D., The, B.S., Paulino, A.C., 2013. Rhabdomyosarcoma arising in a previously irradiated field: an analysis of 43 patients. International Journal of Radiation Oncology – Biology –. Physics 1;85(3), 598–603. https://doi.org/10.1016/j.ijrobp.2012.06.011.

Gladdy, R.A., Qin, L.X., Moraco, N., Edgar, M.A., Antonescu, C.R., Alektiar, K.M., Brennan, M.F., Singer, S., 2010. Do Radiation-associated Soft Tissue Sarcomas have the same prognosis as sporadic soft tissue sarcomas? J. Clini. Oncol. 28 (12), 2064–2069. https://doi.org/10.1200/JCO.2009.25.1728.

Hall, E.J., 2006. Intensity-modulated radiation therapy, protons, and the risk of second cancers. Int. J. Radiat. Oncol. Biol. Phys. 65, 1–7.

Lee, C.L.R., Chang, T.C., Shueh, S., Soong, Y.K., 1990. Rhabdomyosarcoma Following Radiation Therapy for Cervical Carcinoma – A Case Report. Changgeng yi xue za zhi. 20;13(1), 65–71.

Mark, R. J. , Poen, J., Tran, L. M., Fu, Y. S., Heaps, J., & Parker, R. G. (1996). Postirradiation Sarcoma of the Gynecologic Tract: A Report of 13 Cases and a Discussion of the Risk of Radiation-Induced Gynecologic Malignancies. (1996). American Journal of Clinical Oncology, 19(1), 59-64. DOI: 10.1097/00000421-199602000-00013.

Mindell, E.R., Shah, N.K., Webster, J.H., 1997. Postradiation Saroma of Bone and Soft Tissues. Orthopedic Clin. North Am. 8 (4), 821–834.

Murray, E.M., Werner, D., Greff, E.A., Taylor, D.A., 1999. Postradiation sarcomas: 20 cases and a literature review. Int. J. Radiat. Oncol. Biol. Phys. 45, 951–961.

Rubino, C., Shamsaldin, A., Lê, M.G., Labbé, M., Guinebretière, J.M., Chavaudra, J., de Vathaire, F., 2005. Radiation dose and risk of soft tissue and bone sarcoma after breast cancer treatment. Breast Cancer Res Treat. 89, 277–288.

Samartzis, D., Nishi, N., Cologne, J., Funamoto, S., Hayashi, M., Kodama, K., Miles, E.F., Suyama, A., Soda, M., Kasagi, F., 2013. Ionizing radiation exposure and the development of soft-tissue sarcomas in atomic-bomb survivors. J. Bone Joint Surg. Am. 95, 222–229.