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Osteosarcoma of the Humerus Developing as Second Malignancy in the Irradiation Field Outside the Primary Tumor: 11 Years after Ewing Sarcoma of the Scapula and 29 Years after Breast Cancer

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Abstract

Purpose: Development of sarcoma is a known late rare negative side effect of radiotherapy. We add two cases to emphasize the need for open-end follow-up and critical evaluation to avoid misinterpretation. **Patients, Methods, and Results:** Two patients developed osteosarcoma as a second malignancy in the humerus after adjuvant radiotherapy of a primary tumor not directly involving the later affected bone. The first patient had a Ewing sarcoma of the scapula at age 13 years. Though after neoadjuvant chemotherapy the resected specimen showed only fibrotic necrotic areas within clear resection margins, the study group indicated adjuvant radiotherapy in a field including the shoulder joint. At age 24 years she developed an osteosarcoma of the humeral head, which was resected and reconstructed with a proximal humerus endoprosthesis. She is alive without disease at age 32 years. The second patient presented with an osteosarcoma of the proximal humerus 29 years after irradiation for breast cancer including the shoulder joint. The sarcoma was misinterpreted as radiation-induced necrosis and the patient was treated with a reverse shoulder endoprosthesis. Pathologic examination of the resected humeral head then showed a typical osteosarcoma. Two years later the humeral reverse shoulder implant was resected and a proximal humerus tumor prosthesis implanted leaving the original glenosphere. **Conclusions:** In both cases radiation-induced osteosarcoma developed in bone not affected by the

primary cancer. Protecting uninvolved structures must be warranted in the planning of radiotherapy. The long latency between the primary and second cancer mandates long-term—best indefinite—follow-up, as with appropriate treatment of a radiation-induced osteosarcoma good healing rates comparable to those of primary osteosarcoma can still be achieved.

Keywords

Radiation-Induced Osteosarcoma, Ewing Sarcoma, Breast Cancer, Humerus

1. Introduction

Osteosarcoma is a typical second primary cancer occurring during the first 20 years following treatment for a solid cancer in childhood, with Ewing sarcoma patients being especially susceptible [1].

The development of sarcomas after radiotherapy is a well-known complication usually occurring after a latency of over 10 years [2]. The latency of radiation-induced Osteosarcoma (RIOS) in a paediatric population ranged from 5.3 to 29.4 years [3]. In a literature review 109 cases of RIOS after childhood cancer were collected [4].

The patient with a Ewing sarcoma of the scapula reported herein is of special interest as she developed RIOS in the humeral head 11 years after adjuvant irradiation of the scapular resection bed including the shoulder joint.

RIOS usually develops in the vicinity of the treated primary tumor. Fortunately, RIOS is a rare event [5] and therefore may not be considered and misinterpreted as e.g. osteonecrosis [6].

The cases are presented to underline the importance of open-end follow-up of patients treated for malignancies to early recognize and treat adverse effects of therapeutic measures and second tumors.

2. Case Reports

2.1. Case 1 (M.M. *24.03.1991)

At age 13 years (February 2004) a biopsy of a scapular process showed a Ewing Sarcoma. CT revealed a solitary lung metastasis of the left lower lobe. The patient received neoadjuvant chemotherapy according to EURO-E.W.I.N.G. 99 [7]. The lung metastasis was resected through open thoracotomy 4 months after the initial diagnosis. Pathologic examination demonstrated nests of vital tumor within mostly fibrotic devitalized tissue. Subtotal scapulectomy was performed 1.5 months later leaving the supraspinal parts with the glenoid. Pathologic examination revealed uncontaminated resection margins without any vital rests of the Ewing sarcoma. Chemotherapy was continued postoperatively to reach the full course of the protocol. The scapula including the shoulder joint was irra-

diated 2 months after the scapulectomy with 44.8 Gy according to the study group recommendation.

The patient adapted well to the mild restrictions of her shoulder function with abduction to about 100˚.

Chronic pulmonary infections led to a complete left pneumonectomy in 2010 (pathologically no residuals of the Ewing sarcoma).

Early in 2015 the patient developed incapacitating pain in the right shoulder. X-Rays showed an osteolysis of the humeral head (**Figure 1(a)**, **Figure 1(b)**), MRI documented a solid mass with extraosseous subdeltoid extension without signs of intraarticular infiltration (**Figure 1(c)**, **Figure 1(d)**). PET-CT documented FDG-avidity within the osteolytic area (**Figure 1(e)**), but no indication of other lesions. Core needle biopsy was diagnosed as a high grade pleomorphic spindle cell sarcoma with osteosarcomatous differentiation (**Figure 2**). Aspiration of the joint revealed clear synovial fluid. After discussion of various treatment options including complete extraarticular shoulder joint resection [8] and forequarter amputation the patient opted for a transarticular resection of the proximal humerus, which could be offered in the light of clear synovial fluid. Wide resection was performed as illustrated in **Figures 3-5** including the joint

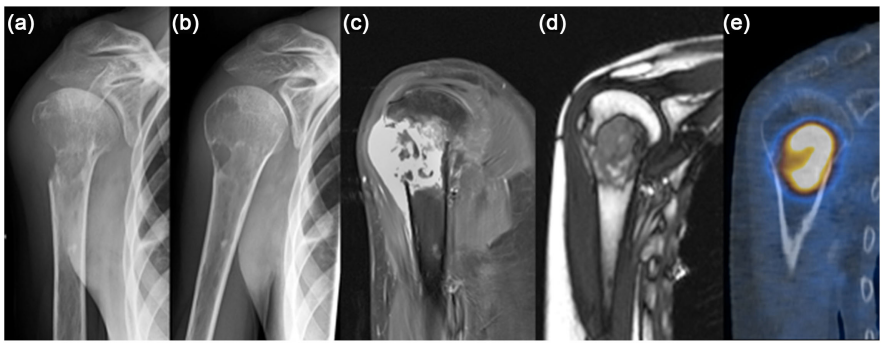

Figure 1. Radiation induced osteosarcoma proximal humerus 11 years after treatment of Ewing sarcoma of the scapula. X-Ray (a, b) showing the osteolysis, MRI t1 fs (c) and t2 trufi (d) the expansion of the osteosarcoma, FDG-PET-CT (e) the intensive uptake.

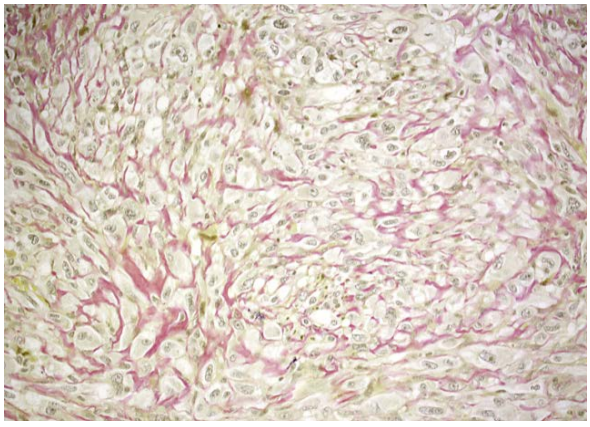

Figure 2. Biopsy Case 1: Pleomorphic mesenchymal neoplasm with osteoid formation diagnostic of osteosarcoma. EVG—staining, magnification 20×.

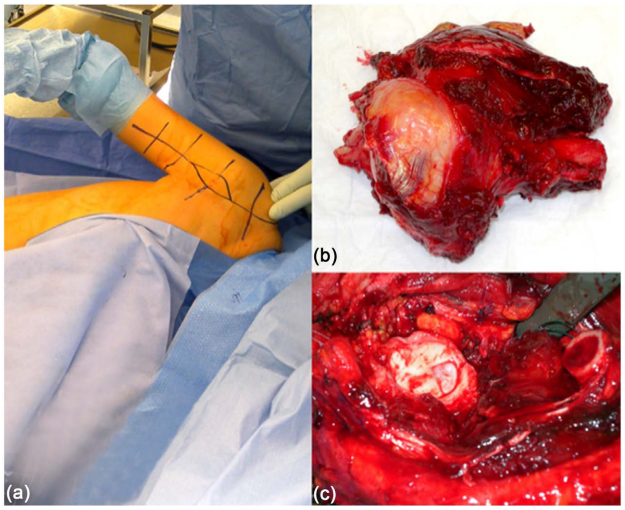

Figure 3. Preparation of the patient for the delto-pectoral approach (a), resected specimen (b), and the defect after resection (c).

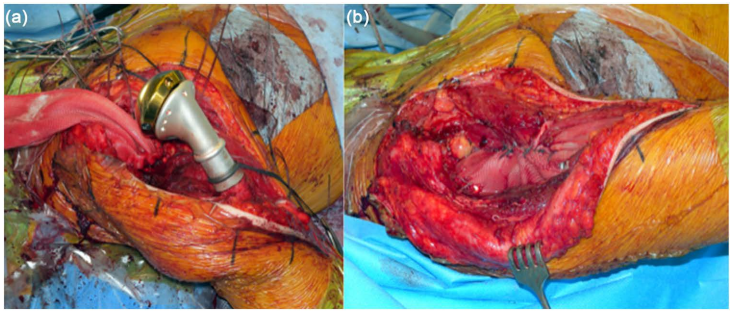

Figure 4. Reconstruction of the resected segment by MUTARS® hemi-prosthesis (a) and stabilization with MUTARS® attachment tube (b).

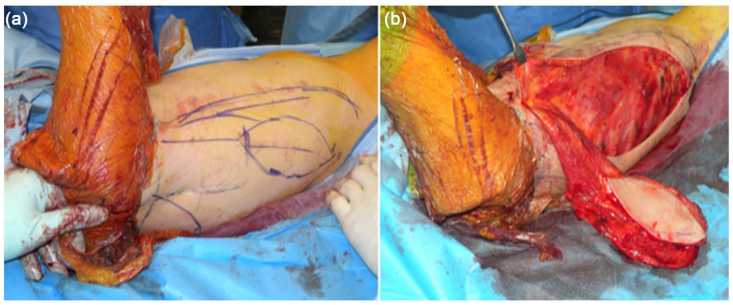

Figure 5. Covering of the defect by pedicled myo-cutaneous M. latissimus dorsi, Incision planned (a), rased flap (b).

capsule, infiltrated deltoid muscle areas and axillary nerve and vessels. The proximal humerus was reconstructed with a MUTARS® Proximal Humeral Replacement (implantcast®) stabilized by a MUTARS® attachement tube (implantcast®) for reconstruction of the capsule and fixation of soft tissue. Soft tissue coverage was achieved by a pedicled M. latissimus dorsi transposition (**Figure 4**). Extralesional resection margins were achieved as shown in **Figure 6**. Chemotherapy therapy was precluded due to the cardio-pulmonary limitations.

Healing was uneventful. At 8 years follow-up the reconstruction remained stable (Figure 7); the patient is free of tumor recurrence or metastases and highly satisfied with the function (Figure 8) pursuing her profession as primary school teacher and being able to follow physical activities limited merely by pulmonary restriction.

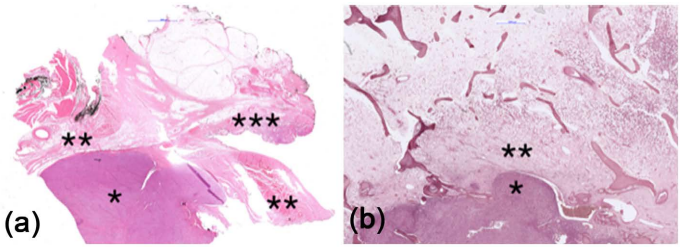

Figure 6. Resection specimen Case 1 demonstrating tumour free resection margins towards the capsule (Figure a) [* vital tumor, ** capsule, *** synovial membrane] and towards healthy bone (b) [* vital tumor, ** healthy bone marrow]. HE staining, magnification 1×.

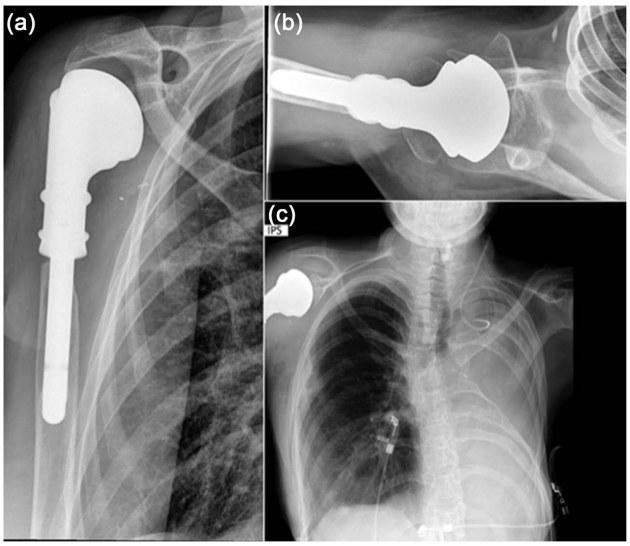

Figure 7. X-Rays at 8 years follow-up documenting the stable well centered reconstruct (a, b). Thorax X-Ray after pneumonectomy (c) following earlier complications of metastasectomy.

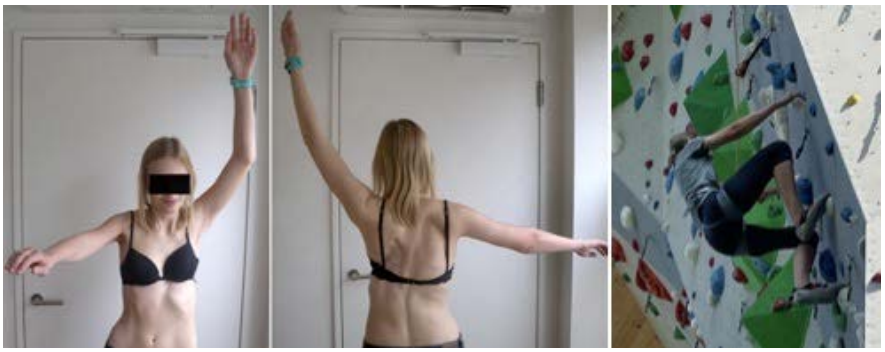

Figure 8. Shoulder function at 8 years follow-up, Screen-shot of the climbing video.

2.2. Case 2 (C.W. *01.03.1953)

In 1986 the patient was diagnosed with breast cancer and treated with local resection. A local recurrence of breast cancer was treated in 1992 by local resection. Adjuvant radiotherapy to the thoracic wall 60 Gy including 46.4 Gy to the axilla and shoulder joint was given. In 2021 images of the left shoulder (**Figure 9**) were interpreted as radiation-induced necrosis. Treatment with inverse shoulder replacement was performed at a foreign hospital (**Figure 10(a)**). The pathologic examination of the resected humeral head demonstrated RIOS. An offer of forequarter amputation was refused by the patient. Standard X-Ray follow-up revealed progressive destruction of the greater tubercle over the following 2 years (**Figure 10(b)**). Biopsy proved the same osteosarcomatous pathology as at shoulder replacement leading to a second-opinion consultation with us. According to our discussion of different options the patient was treated at the

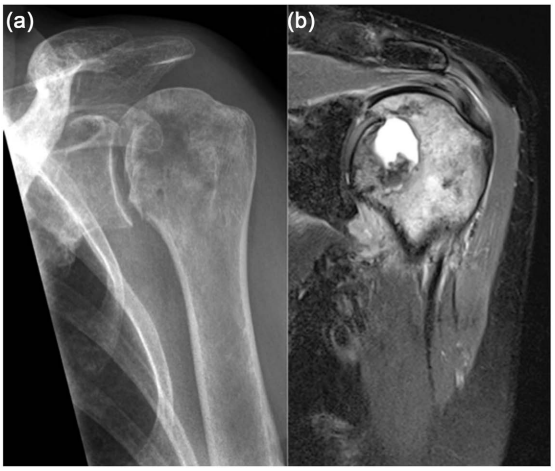

Figure 9. Radiation sarcoma misdiagnosed as osteonecrosis 29 years after irradiation for breast cancer. X-Ray showing osteolysis and subchondral collaps (a), and MRI changes (b).

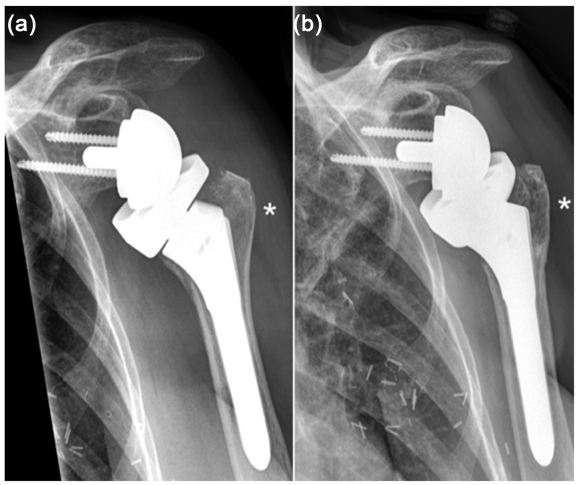

Figure 10. X-Rays after inverse shoulder replacement in 2021 (a) and 2023 (b) showing the increasing osteolysis in the greater tuberosity (*) caused by the growing radiation-induced osteosarcoma confirmed by biopsy.

primary institution by resection of the endoprosthetic complex and replacement by a "megaprosthesis" reconstruction in May 2023. According to the pathology report an extralesional resection was achieved.

3. Discussion

Radiotherapy plays an important role in the treatment of sarcomas, and is an integral modality in Ewing sarcoma [9]. However, radiotherapy and chemotherapy are associated with excessive risk for a second sarcoma, especially among younger patients; in a cohort study of 1.5 million person-years, the risk ratio to develop a secondary soft tissue or bone sarcoma at 15 years follow-up increased by a factor of about 3 to 4 [10]. Among different types of radiation-induced sarcomas RIOS accounts for over 50% [11] [12]. It seems that Ewing patients are at special risk to develop second malignancies [13], with a high proportion of RIOS; among 327 Ewing patients with second malignancies, 19% were osteosarcomas [13]. Most patients developing second malignancy evidently had received radiotherapy [14]. From most case reports of RIOS as second malignancy after Ewing sarcoma it can be assumed that they developed within the affected bone treated by irradiation [15]. When confronted with abnormal musculoskeletal findings developing after treatment of primary tumors biopsy needs to be generously considered [16] especially considering the low risk of percutaneous biopsy [17]. With healing rates of RIOS close to those of primary osteosarcoma aggressive diagnostics and treatment are indicated [12].

Both cases presented here are of interest as the RIOS developed in bones not primarily affected but lying within the radiation field. Thus they need to be considered as probably avoidable complications. The restrictive planning of the radiation field therefore seems to be of utmost importance.

4. Conclusion

The latency between the primary cancer and development of RIOS at 11, respectively 29 years supports the known need for longer—best indefinite—follow-up of these patients in the light of healing results of RIOS near to those of primary osteosarcoma.

Ethical Approval

The study was approved by the Institutional review boards.

Informed Consent

The patients have been informed about the study and agreed to submission of their cases for publication. All details and radiographic images have been deidentified to protect patient confidentiality.

Authors Contributions

The last author collected the data. All authors contributed equally to the evalua-

tion and interpretation of the data, and finalizing the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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