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Title: Post-radiation extra-skeletal osteosarcoma

Clinical History: This 46-year-old female presented to ophthalmology with a painful left eye and blurred vision. CT imaging revealed a focus of enhancement and surrounding oedema in the left inferior frontal lobe that was not visible on previous routine surveillance imaging 3 months ago. Subsequent MRI showed an extra-axial soft tissue mass in the left anterior cranial fossa that was contiguous with a tumour in the left orbital apex. The patient had a past medical history of glioblastoma 12 years ago treated with irradiation (60Gy) and the clinical and radiological suspicion was recurrent glioblastoma.

Ophthalmic Pathology
Macro:Two fragments of firm white tissue, the larger 10 x 5 x 5 mm
Microscopy:Sections show a high grade malignant tumour composed of polygonal cells with clear cytoplasm and prominent cell borders. The cells are pleomorphic with numerous mitotic figures (often atypical). Throughout the tumour there are areas with lace-like osteoid matrix. The appearances are those of a high-grade osteosarcoma.

Discussion
This patient is the longest surviving chemoradiotherapy patient with glioblastoma in Glasgow. She went on to develop an osteosarcoma in the orbit. The bulk of the tumour was in the soft tissues with no periosteal attachment on MRI and was therefore considered an extraskeletal osteosarcoma (ESOS). These are rare tumours that constitute less than 4% of all osteosarcomas and are more commonpost-irradiation[1]. Previous trauma is also a risk factor. The extremities, girdle, and retroperitoneum are most involved. Orbital involvement is exceedingly rare, with 5 cases reported in the literature[2-6]. Three of the patients hadno known risk factors and presumed *de novo* tumours.

One patient, an 11-year-old boy, developed orbital ESOS after radiotherapy for retinoblastoma[2]; and Fan et al report orbital ESOS in a 78-year-old man occurring 12 months after excision of a left medial canthal basal cell carcinoma that was followed by adjuvant radiotherapy[4]. Despite the short latency period, the authors suggested this was likely to be a post-radiation sarcoma (PRS). This case is the sixth case of orbital ESOS to be reported in the literature and the third to be classified as PRS.

PRS is a well-known, serious, and long-term treatment complication of radiotherapy that is estimated to account for between 2.5% - 5.5% of all sarcomas[1, 7-12]. The overall incidence is estimated to be less than 1%, but because of the potentially long latency period (1 – 50 years, with a reported mean latency of between 10 and 20 years[7]) and required long-term follow-up, it is likely cases are missed and therefore these figures are probably an underestimate.

Diagnostic criteria for PRS were originally defined by Cahan et al in 1948[13]and have since been modified by Murray et al to allow for the inclusion of post-irradiation soft tissue sarcomas and a shorter latency period[7]. There is no agreed minimum latency period between irradiation and tumour development. However, it is generally considered that tumours appearing less than 2 years following irradiation are unlikely to be radiation induced.

Risk factors include genetic predisposition (e.g., germline mutations in Rb1 and p53 tumour suppressor genes, in the case of retinoblastoma and Li–Fraumeni syndrome, respectively), young age at treatment, and concomitant chemotherapy. The total dose of radiation appears to influence tumour incidence and most PRS are reported to occur at doses of 50Gy or more. There is, however, no agreed safe threshold in terms of dose below which there is zero risk of developing a secondary malignancy. This patient had received 60Gy as well as chemotherapy with temozolomide.

PRS are less heterogeneous than spontaneously occurring sarcomas. The most common tumour type is pleomorphic undifferentiated sarcoma (previously malignant fibrous histiocytoma), which accounts for approximately 70% of cases, followed by osteosarcoma, fibrosarcoma, malignant peripheral nerve sheath tumour, chondrosarcoma and angiosarcoma.

Prognosis is poor compared with their *de novo* counterparts[14]. There are several possible reasons for this. PRS are usually more aggressive and tend to be diagnosed at a more advanced stage[15]. Delay in diagnosis and initial misdiagnosis have also been shown to be contributing factors[15, 16]. Unlike *de novo* sarcomas, most arise in central locations precluding radical surgery: patients with PRS of the extremities have the best survival (30% at 5 years) whereas those with lesions arising in the vertebral column, pelvis, and shoulder girdle have survival rates of less than 5% at 5 years. The wide variation in these 5-year survival rates reflects resectability. Several large studies have shown that obtaining negative margins is difficult and the subsequent risk of local recurrence is high, estimated at 45%[1, 17]. And finally, adjuvant treatment options are limited: radiotherapy is often impossible because of the dangers of irradiating a previously irradiated field, and PRS show poor sensitivity to chemotherapy[7]. Many of these factors contributed to a poor outcome in this patient who died of her disease 3 months later.

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