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CASE BASED REVIEWS

Osteosarcoma and second malignant neoplasms: a case series

R. L. Geary[1] · L. R. Corrigan[1] · D. N. Carney[1] · M. J. Higgins[1]

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Abstract

Background The overall survival of patients with localised osteosarcoma has dramatically improved with the introduction of multi-drug chemotherapeutic regimens into the treatment paradigm. However, despite optimal treatment, all-cause mortality remains higher among osteosarcoma survivors than in the general population. The development of second malignant neoplasms contributes to this higher mortality rate.

Case series We present three cases of patients definitively treated for osteosarcoma who subsequently developed a second malignant neoplasm. The first case describes a 17-year-old female with osteosarcoma of her right femur treated with surgical resection and perioperative chemotherapy. Ten years later, she was diagnosed with metastatic HER2-positive breast cancer. Genetic testing identified a germline TP53 mutation, confirming the presence of Li-Fraumeni syndrome. The second case details an 18-year-old male with osteosarcoma of his right humerus treated with definitive resection and perioperative chemotherapy. He was diagnosed with appendiceal adenocarcinoma after presenting with acute abdominal pain 17 years later. The third case reviewed is of a 36-year-old male with osteosarcoma of his right femur treated with definitive resection and adjuvant chemotherapy. A diagnosis of leiomyosarcoma was made 7 years later following surveillance imaging.

Discussion The risk of second malignant neoplasms in osteosarcoma may relate to previous oncological treatment, an inherited cancer predisposition syndrome or a spontaneous new neoplasm. Although screening for a second malignancy is not routinely recommended for osteosarcoma survivors, a high degree of clinical suspicion should be maintained during surveillance.

Keywords Osteosarcoma · Second primary

Introduction

Osteosarcoma is a primary malignant bone tumour characterised by the production of osteoid and/or immature bone. It represents the most common malignant tumour of bone, accounting for 30% of bone tumour cases in Ireland. Overall, it remains a rare malignancy [1]. Osteosarcoma has a bimodal incidence, predominantly affecting children and adolescents (primary osteosarcomas), with a second peak in incidence in adults over the age of 65 (frequently secondary osteosarcomas—i.e., arising from sarcomatous change within a benign bone lesion). Optimal definitive treatment involves a combination of surgery and perioperative chemotherapy [2]. With the introduction of multidrug chemotherapeutic regimens into the treatment paradigm, overall survival (OS) has dramatically improved with an expected 5-year OS in the region of 70% for localised disease treated with three drug regimens [3, 4].

Surveillance and survivorship care are important components of oncological management for this cohort, particularly, given the young age at diagnosis for many. Despite optimal multimodality treatment, recurrent cancer is the most likely cause of death among patients with osteogenic sarcoma. A small number, however, will develop a new primary cancer (second malignant neoplasm/SMN) which may relate to previous oncological treatment or an inherited cancer predisposition syndrome. Here, we present a case series of three patients who survived their osteosarcoma but subsequently developed a second malignant neoplasm.

Case Reports

Case 1

A 17-year-old Irish female presented with high-grade osteogenic sarcoma of her right femur. A right above-knee amputation with perioperative (neoadjuvant and adjuvant) MAP

✉ R. L. Geary
gearyr@tcd.ie

[1] Department of Medical Oncology, Mater Misericordiae University Hospital, DublinD07 R2WY, Ireland

chemotherapy (high-dose methotrexate alternating with doxorubicin and cisplatin) was performed. The surgical specimen showed 80% necrosis of malignant cells. The following year, and again 24 months later, she developed oligometastatic disease in her lungs and underwent two surgical metastasectomies with interval etoposide/ifosfamide chemotherapy. This cancer has not recurred in 10 years since.

At the age of 25 (8 years after her diagnosis and after receiving a total lifetime dose of 300 mg/m^2 of doxorubicin chemotherapy), the patient reported shortness of breath whilst walking her dogs and was found to have a significant anthracycline-related cardiomyopathy. She has been under the care of the heart failure service since that time and has recovered her ejection fraction with optimal medical management.

At the age of 27, the patient developed a right breast mass and hepatic lesions were identified on CT imaging. A liver biopsy was performed revealing a poorly differentiated carcinoma with HER-2 overexpression. Immunohistochemistry for P53 was negative. PET CT identified a 3.5-cm mass in the right breast and biopsy confirmed a grade 3 invasive ductal carcinoma, ER/PR negative, and HER2 positive. She was diagnosed with metastatic breast cancer and commenced on paclitaxel and trastuzumab (further HER-2-targeting treatment was withheld due to risk of exacerbating her cardiac impairment).

Family history was significant for a maternal granduncle with bowel cancer in his 60s, a maternal granduncle with oesophageal cancer in his 60s, and a maternal great grandmother with eye cancer, presumed ocular melanoma. Paternal family history was unknown.

This patient was referred for genetic evaluation and counselling. A germline TP53 mutation was identified confirming the presence of Li-Fraumeni syndrome.

Case 2

An 18-year-old Irish male was diagnosed with high-grade osteogenic sarcoma of his right humerus in 1998. This was treated with a combination of surgical resection and perioperative MAP chemotherapy with 100% necrosis seen on the surgical specimen. Five years later, he had an isolated pulmonary metastasis which was surgically removed and treated with adjuvant chemotherapy. He had a subsequent resection of a large mediastinal mass (dedifferentiated osteosarcoma) 8 years after initial diagnosis followed by further chemotherapy.

Family history was significant for a maternal aunt with pancreatic cancer in her 60s, a maternal first cousin with breast cancer at the age of 30, and a paternal first cousin with mandibular bone cancer in his 40s.

Seventeen years following his initial diagnosis, aged 35, he presented with abdominal pain and proceeded to have a laparoscopic appendectomy. On histological examination of the postoperative specimen, an invasive well-differentiated adenocarcinoma was identified. The surgical margins were clear and associated lymph nodes were negative; therefore, no adjuvant chemotherapy was warranted.

The patient was referred for genetic counselling, and peripheral blood was screened for the presence of a germline mutation in either the p53 tumour suppressor gene or a mismatch repair gene that could relate to Lynch syndrome. No causative mutation was identified. At this time, the patient is alive and cancer free. Both tumours appear to have been sporadic in nature.

Case 3

A 36-year-old never smoker, Irish male was first diagnosed with high-grade, chondroblastic, osteogenic sarcoma of the right femur in 2003. He proceeded to amputation and 8 cycles of adjuvant MAP.

Family history was significant for maternal breast cancer in her 60s and paternal colorectal cancer in his 70s. There was no other significant family history.

Surveillance imaging 7 years later revealed an 8-cm retroperitoneal pelvic nodal mass involving the inferior vena cava. Biopsy identified this as a second primary, high-grade leiomyosarcoma. This was different morphologically and by immunohistochemistry to the patient's previous osteosarcoma. Immunohistochemistry revealed an absence of p53 staining in both the leiomyosarcoma and previous osteosarcoma but could not differentiate between loss due to germline or somatic mutation. This patient did not proceed to germline testing.

The patient was treated with neoadjuvant etoposide and ifosfamide and underwent surgical resection and subsequent adjuvant radiotherapy due to positive surgical margins.

Over the subsequent years, he developed unresectable lung metastases secondary to leiomyosarcoma, which ultimately progressed despite several lines of palliative chemotherapy and targeted systemic approaches. The patient died at age 50, 5 years after the diagnosis of his second cancer.

Discussion

Our case series illustrates the potential for late development of new, unrelated cancers in patients who have completed definitive treatment for osteogenic sarcoma. All of these cases occurred 5 years or more from diagnosis of primary osteosarcoma, in itself a rare tumour. Whilst recurrence of osteosarcoma is the major mitigating factor for long-term survival in these patients, it tends to occur within the first 5 years following treatment with rates of late recurrence (5 or more years after diagnosis) ranging

Table 1 Observed primary sites of SMN

Primary site	SIR Fidler et al. (CI) [7]	SIR Nagarajan et al. (CI) [9]	Percentage of observed SMN Fidler et al.	Percentage of observed SMN Nagarajan et al.
Breast	4.0 (1.8–8.8)	9.73 (5.56–15.80)	26%	32.7%
Skin	NR	4.84 (2.09–9.55)	NR	16.3%
GI	NR	5.84 (2.13–12.70)	NR	12.2%
Thyroid	NR	7.03 (2.57–15.30)	NR	12.2%
STS/bone	*65.4 (21.1–202.-7)	13.72 (3.69, 35.12)	13%	8.2%

SIR, standardised incidence ratio; *CI*, 95% confidence interval; *SMN*, second malignant neoplasm; *Bone only

from only 1.4 to 5.7% in the literature [5, 6]. All-cause mortality for osteosarcoma survivors who have survived their diagnosis by more than 5 years remains significantly higher than the general population [7]. Late recurrence of osteosarcoma is the main cause of the raised mortality but second cancers represent a significant minority of cases.

Osteosarcoma is a relatively rare malignancy and surveillance data are limited. However, several groups have made efforts to collate long-term outcomes on these patients. The largest available results come from the Childhood Cancer Survivor Study (CCSS) which was a multi-institutional study of over 20,000 individuals surviving 5 or more years following treatment for childhood cancer, 1077 (5.2%) of whom had osteosarcoma [8]. In the subset of childhood osteosarcoma patients that survived more than 5 years, 7% (75 out of 1068), ultimately died from recurrent or persistent osteosarcoma [9]. The cumulative incidence of SMNs at 25 years in osteosarcoma survivors who completed long-term follow-up was 5.4%, with a standardised incidence ratio (SIR) of 4.79 (95% confidence interval (CI) 3.54–6.33; $p < 0.01$) as compared to the general population (Surveillance, Epidemiology, and End Results (SEER) registry rates).

Similarly, Fidler et al. studied 664 patients, who participated in the British Childhood Cancer Survivor Study (BCCSS), diagnosed with any bone sarcoma before the age of 15, from 1940 to 1991, who survived more than 5 years from diagnosis [7]. They found that the death rate among patients diagnosed with osteosarcoma was 6 times higher than the general population. The majority is explained by late recurrence of disease; however, the development of a SMN was the second most common cause of death in osteosarcoma survivors.

Across several reports, the SIR for the development of a second malignancy among osteosarcoma survivors has been reported as 2.4–4.6, with a slight female predominance and a higher incidence among patients whose primary osteosarcoma involved the axial skeleton [7, 9–11]. Table 1 shows the primary site of secondary malignancies.

There are a number of possible explanations for the link between primary osteosarcoma and the higher risk of developing a second malignancy. These may be due to adverse long-term effects of therapy used in the primary treatment of osteosarcoma, they may be due to genetic predisposing factors, and finally, they may of course represent spontaneous new second malignancies with no identifiable cause.

Both radiotherapy and chemotherapeutic agents have been implicated in the development of SMNs. Armstrong et al. examined 2821 deaths in all childhood cancer survivors, 470 of which were due to second malignancy [12]. The use of alkylating chemotherapies (such as cyclophosphamide) and high doses of epipodophyllotoxins (such as etoposide) were both associated with an increased risk of death from SMN. Etoposide is commonly used in the treatment of osteosarcoma [13]. Methotrexate and doxorubicin are also associated with the development of second cancers including haematological malignancies [14, 15].

Radiotherapy is an established risk factor for second primary neoplasm and has been linked to the development of secondary tumours in up to 8% of solid tumour survivors [12, 16]. Radiotherapy is used rarely in the treatment of osteosarcoma in Ireland and because the treatment field is usually anatomically confined to the limbs in osteosarcoma, it is less likely to be contributory [1].

Osteosarcoma may be the presenting diagnosis of a hereditary cancer predisposition syndrome. Li-Fraumeni syndrome (LFS) is a rare autosomal dominant condition that is associated with germline TP53 mutations. TP53 is a tumour suppressor gene with an important role in regulating cells with DNA damage. LFS is manifested by the development of multiple malignant neoplasms at an early age including sarcoma, breast cancer (which is usually HER2 overexpressing), brain tumours, leukaemia, and adrenal cancer [17, 18]. Immunohistochemistry for p53 protein was negative in our third patients' tumours. Loss of p53 staining indicates a loss of the whole protein or loss of functional protein unit but does not definitively diagnose whether the patient has a germline (hereditary) mutation in

p53 or a somatic p53 mutation (loss of p53 within tumour cells only, therefore not hereditary). Somatic p53 mutations are a common finding in many cancers including sarcomas.

Ballinger et al. recently performed exon sequencing on 72 genes associated with increased cancer risk on 1162 patients with sarcoma [19]. They found that over half of patients with sarcoma have putatively pathogenic variation in known and novel cancer genes including TP53, ATM, ATR, BRCA2, and ERCC2 [19]. Early referral of young patients with sarcoma for germline genetic testing regardless of age/family history would facilitate risk stratification of patients and help to identify not only patients who would benefit from additional surveillance for SNMs but also counselling and screening of unaffected family members [20–22].

Our case series illustrates the rare but recognised occurrence of SMNs in osteosarcoma survivors. Surveillance in this patient cohort is not only important for early detection of osteosarcoma recurrence but also for the detection of secondary malignancies and late complications associated with systemic therapy. International expert guidelines recommend surveillance with a physical exam, full blood count, imaging of the primary site and chest every 3 months for years 1 and 2, every 4 months for years 2 and 3, every 6 months for years 4 and 5, and yearly thereafter for those with a history of osteosarcoma [13]. Whilst not yet available in Ireland, these relatively rare cancer patients should optimally be followed in specialised clinics to encompass survivorship health maintenance and to ensure clinical and radiological surveillance for detection of late recurrences and SMN. We also recommend the integration of hereditary cancer expertise into the multidisciplinary management of osteosarcoma.

Compliance with ethical standards

This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest The authors declare that there are no conflicts of interest.

References

1. Deady S (2014) Primary bone cancer. National Cancer Registry Ireland. https://www.ncri.ie/sites/ncri/files/pubs/Bones.pdf. Accessed 10 February 2019
2. Goorin AM, Schwartzentruber DJ, Devidas M, Gebhardt MC, Ayala AG, Harris MB, Helman LJ, Grier HE, Link MP (2003) Presurgical chemotherapy compared with immediate surgery and adjuvant chemotherapy for nonmetastatic osteosarcoma: Pediatric Oncology Group Study POG-8651. J Clin Oncol 21(8):1574–1580
3. O'Kane GM, Cadoo KA, Walsh EM et al (2015) Perioperative chemotherapy in the treatment of osteosarcoma: a 26-year single institution review. Clin Sarcoma Res 5:17. https://doi.org/10.1186/s13569-015-0032-0
4. Anninga JK, Gelderblom H, Fiocco M, Kroep JR, Taminiau AHM, Hogendoorn PCW, Egeler RM (2011) Chemotherapeutic adjuvant treatment for osteosarcoma: where do we stand? Eur J Cancer 47(16):2431–2445. https://doi.org/10.1016/j.ejca.2011.05.030
5. Gelderblom H, Jinks RC, Sydes M, Bramwell VHC, van Glabbeke M, Grimer RJ, Hogendoorn PCW, McTiernan A, Lewis IJ, Nooij MA, Taminiau AHM, Whelan J (2011) Survival after recurrent osteosarcoma: data from 3 European Osteosarcoma Intergroup (EOI) randomized controlled trials. Eur J Cancer 47(6):895–902. https://doi.org/10.1016/j.ejca.2010.11.036
6. Kempf-Bielack B, Bielack SS, Jurgens H et al (2005) Osteosarcoma relapse after combined modality therapy: an analysis of unselected patients in the Cooperative Osteosarcoma Study Group (COSS). J Clin Oncol 23(3):559–568
7. Fidler MM, Frobisher C, Guha J et al (2015) Long-term adverse outcomes in survivors of childhood bone sarcoma: the British Childhood Cancer Survivor Study. Br J Cancer 112(12):1857–1865. https://doi.org/10.1038/bjc.2015.159
8. Robison LL, Mertens AC, Boice JD, Breslow NE, Donaldson SS, Green DM, Li FP, Meadows AT, Mulvihill JJ, Neglia JP, Nesbit ME, Packer RJ, Potter JD, Sklar CA, Smith MA, Stovall M, Strong LC, Yasui Y, Zeltzer LK (2002) Study design and cohort characteristics of the Childhood Cancer Survivor Study: a multi-institutional collaborative project. Med Pediatr Oncol 38(4):229–239
9. Nagarajan R, Kamruzzaman A, Ness KK, Marchese VG, Sklar C, Mertens A, Yasui Y, Robison LL, Marina N (2011) Twenty years of follow-up of survivors of childhood osteosarcoma: a report from the Childhood Cancer Survivor Study. Cancer 117(3):625–634. https://doi.org/10.1002/cncr.25446
10. Hauben EI, Arends J, Vandenbroucke JP, van Asperen CJ, van Marck E, Hogendoorn PCW (2003) Multiple primary malignancies in osteosarcoma patients. Incidence and predictive value of osteosarcoma subtype for cancer syndromes related with osteosarcoma. Eur J Hum Genet 11(8):611–618
11. Aung L, Gorlick RG, Shi W, Thaler H, Shorter NA, Healey JH, Huvos AG, Meyers PA (2002) Second malignant neoplasms in long-term survivors of osteosarcoma: Memorial Sloan-Kettering Cancer Center experience. Cancer 95(8):1728–1734
12. Armstrong GT, Liu Q, Yasui Y, Neglia JP, Leisenring W, Robison LL, Mertens AC (2009) Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study. J Clin Oncol 27(14):2328–2338. https://doi.org/10.1200/JCO.2008.21.1425
13. Biermann J (2019) Bone cancer: NCCN clinical practice guidelines in oncology. National comprehensive cancer network. https://www.nccn.org/professionals/physician_gls/pdf/bone.pdf. Accessed 10 Feb 2019
14. Al-anazi K, Eltayeb K, Bakr M (2009) Methotrexate-induced acute leukaemia: report of three cases and review of the literature. Clin Med Case Rep 2:43–49
15. Le Deely MC, Suzan F, Cutuli B (2007) Anthracyclines, mitoxantrone, radiotherapy and granulocyte colony stimulating factor: risk factors for leukemia and myelodyslastic syndrome after breast cancer. J Clin Oncol 25(3):292–300
16. Berrington de Gonzalez A, Curtis RE, Kry SF et al (2011) Proportion of second cancers attributable to radiotherapy treatment in adults: a cohort study in the US SEER cancer registries. Lancet Oncol 12(4):353–360. https://doi.org/10.1016/S1470-2045(11)70061-4
17. Ognjanovic S, Olivier M, Bergemann TL, Hainaut P (2012) Sarcomas in TP53 germline mutation carriers: a review of the

IARC TP53 database. Cancer 118(5):1387–1396. https://doi.org/10.1002/cncr.26390

18. Olivier M, Goldgar DE, Sodha N et al (2003) Li-Fraumeni and related syndromes: correlation between tumor type, family structure, and TP53 genotype. Cancer Res 63(20):6643–6650
19. Ballinger M, Goode D, Ray-Coquard I et al (2016) Monogenic and polygenic determinants of sarcoma risk : an international genetic study. Lancet Oncol 17(9):1261–1271. https://doi.org/10.1016/S1470-2045(16)30147-4
20. Wong FL, Boice JD Jr, Abramson DH et al (1997) Cancer incidence after retinoblastoma. Radiation dose and sarcoma risk. JAMA 278(15):1262–1267
21. Monnat RJ Jr (2010) Human RECQ helicases: roles in DNA metabolism, mutagenesis and cancer biology. Semin Cancer Biol 20(5):329–339. https://doi.org/10.1016/j.semcancer.2010.10.002
22. Nilbert M, Therkildsen C, Nissen A, Åkerman M, Bernstein I (2009) Sarcomas associated with hereditary nonpolyposis colorectal cancer: broad anatomical and morphological spectrum. Familial Cancer 8(3):209–213. https://doi.org/10.1007/s10689-008-9230-8