Published in final edited form as:

Pediatr Blood Cancer. 2009 September ; 53(3): 496–498. doi:10.1002/pbc.22074.

Secondary Supratentorial Primitive Neuroectodermal Tumor Following Treatment of Childhood Osteosarcoma

Courtney D. Fitzhugh, MD¹, Barbara Wise, CPNP¹, Kristin Baird, MD¹, Maria Tsokos, MD³, Lee Helman, MD¹, Crystal Mackall, MD¹, Sharon A. Savage, MD², and Katherine E. Warren, MD¹

¹Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland ²Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, Maryland ³Laboratory of Pathology, Center for Cancer Research, National Cancer Institute

Abstract

A 16-year-old Caucasian male was diagnosed with a primitive neuroectodermal tumor (PNET) five years following the diagnosis of nonmetastatic osteosarcoma of the left proximal humerus. The patient was initially treated with standard chemotherapy and limb salvage resection for osteosarcoma. Nine months after the completion of therapy, he developed lung metastases for which he underwent surgical resection and received additional chemotherapy. Almost five years after the osteosarcoma diagnosis, the patient was diagnosed with a supratentorial PNET, which represents the first known case reported in a patient with osteosarcoma.

Keywords

osteosarcoma; primitive neuroectodermal tumor; genetic predisposition syndromes

Introduction

Survival in patients with pediatric malignancies has improved dramatically over the past three decades.[1] As a result, a number of long-term toxicities related to treatment are developing, including secondary malignancies.[2] Secondary malignancies result from either genetic predisposition or treatment-related cellular injury, and include lymphomas, leukemias, and solid tumors.[1] Few childhood cancer patients have a defined cancer predisposition syndrome.[1] More commonly, malignancies occur as a result of prolonged immunosuppression[1] or exposure to irradiation and DNA damaging chemotherapy.[3]

Case Description

The patient is a 16-year-old Caucasian male originally diagnosed with non-metastatic osteosarcoma of the left proximal humerus (Figure 1A) four ½ years prior to this presentation. Family history was significant for lung cancer in his paternal grandfather and maternal great-grandmother, who were both smokers, and a paternal uncle with developmental delay and leukemia diagnosed at age 43. The patient received standard

To whom requests for reprints should be addressed: Katherine E. Warren, M.D., Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Building 10, Room 1W-3940, Phone 301-435-4683, Fax 301-451-7052, warrenk@mail.nih.gov.

therapy, including six cycles of doxorubicin and methotrexate with four cycles of cisplatin followed by a limb salvage procedure. Nine months after completing therapy, a right lung nodule was found, resected, and proven to be osteosarcoma. He received eight cycles of ifosfamide (1800 mg/m²/dose for five days) and etoposide (100 mg/m²/dose for five days) over the next six months. He remained disease-free until 11 months after completion of chemotherapy when he underwent resection of a small left lung nodule as well as twenty additional palpable, non-radioapparent nodules. Pathology showed no tumor. Another solitary nodule in his left upper lobe was resected 20 months post chemotherapy completion, and was positive for recurrent osteosarcoma. He had no other evidence of osteosarcoma at that time, and restaging performed one year later showed no evidence of disease.

One month thereafter, 56 months after initial osteosarcoma diagnosis, the patient presented with a two week history of vomiting and headaches, 2 days of decreased mobility of his right toes, and a one day history of right foot drop. Neurologic examination revealed absent right ankle dorsiflexion, inversion, eversion, and right toe paresis. Plantar flexion and sensation in his right ankle and foot were also significantly decreased.

Magnetic resonance imaging (MRI) revealed a left superior frontal mass (Figure 2). Dexamethasone was initiated and the patient underwent a gross total resection without complications. Pathologic examination showed a small round blue cell tumor with many Homer-Wright rosettes (Figure 1B) consistent with a PNET. Tumor cells were positive for neuron specific enolase (NSE). In addition, the tumor cells expressed membranous staining for MIC2 protein (CD99 antibody, Fig. 1C), which is characteristic for peripheral PNET and absent from central PNET. Staining for synaptophysin was focal and weak compared to the positive control slide. Glial differentiation was not observed, and the tumor cells were negative for glial fibrillary acidic protein (GFAP), S-100 protein, CD56, keratin (AE1/3), epithelial membrane antigen (EMA), and CD34. The diagnosis was confirmed by review at two additional institutions. The tumor cells were negative for t(11;22) and t(21;22) by RT-PCR. Cerebrospinal fluid cytopathology was negative for malignant cells. Spine MRI, bone scan, chest CT, and plain film of the left humerus did not show evidence of metastatic PNET or recurrent osteosarcoma.

The occurrence of a second rare cancer in this patient prompted evaluation for a genetic syndrome. Our patient did not have clinical features of syndromes associated with known osteosarcoma risk, such as Werner Syndrome or Rothmund-Thomson Syndrome and did not have a history of retinoblastoma. Finally, *TP53* mutation testing of the patient was performed to evaluate for Li-Fraumeni Syndrome and none were identified.

After surgery, he received craniospinal irradiation therapy (total dose 54/36 Gy), followed by adjuvant chemotherapy with cyclophosphamide (1000 mg/m²/day), cisplatin (75 mg/m²/day), and vincristine (1.5 mg/m²/day). Vincristine was discontinued after cycle two due to peripheral neuropathy. He completed eight cycles of chemotherapy and has no evidence of disease.

Discussion

The most common cause of death in cancer patients who have survived at least five years from their diagnosis is relapse.[4] Excess mortality is also related to treatment-related effects, including the development of secondary malignancies.[1,2] Multiple chemotherapeutic agents, including alkylating agents and topoisomerase II inhibitors, have resulted in secondary malignancies.[3]

The incidence of secondary malignancies in pediatric patients ranges from 1.7-8.6%.[5-9] Of more than 4800 individuals with bone cancers, the cumulative incidence at 25 years of

developing a second malignancy adjusted for the risk of death due to other etiologies was 8.6%.[5] Of greater than 14,000 5-year survivors of childhood cancer enrolled on the Childhood Cancer Survivor Study, 116 subjects (0.8%) developed primary CNS tumors.[8] Of these, 40 patients developed gliomas a median of 9 years from original diagnosis, and 66 patients developed meningiomas 17 years after diagnosis. PNETs arose in 6 patients; initial cancer diagnosis was not specified. Radiation therapy was found to increase the risk of secondary malignancies, with odds ratios ranging from 6.78 to 9.94.[8]

Multiple malignancies have been described in patients originally diagnosed with osteosarcoma with an incidence ranging from 2.2-7%.[7,10] The rate of second malignancy at five, ten, fifteen, and twenty years has been reported to be 1.5%, 4.6%, 4.2%, and 4.5%, respectively[10] and includes lymphoma, leukemia, sarcoma, and carcinoma.[10] Central nervous system neoplasms, including meningioma and high-grade gliomas, have also been reported.

One to ten percent of childhood tumors are associated with cancer predisposition syndromes.[11] Those associated with increased risk of osteosarcoma include Rothmund-Thomson Syndrome, Werner Syndrome, retinoblastoma, and Li-Fraumeni Syndrome. Rothmund-Thomson Syndrome is a rare autosomal recessive disorder associated with a rash, cataracts, skeletal anomalies, and a predisposition for the development of cancers, including osteosarcoma.[12] Werner syndrome is characterized by short stature, premature grayish hair and baldness, atherosclerosis, osteoporosis, juvenile cataracts, and a tendency to develop neoplasms including osteosarcoma.[13] In 1969, Li and Fraumeni described four families in which childhood soft tissue sarcoma was associated with premenopausal breast cancer and other early onset malignancies in their close relatives.[14] Classical Li-Fraumeni Syndrome is defined as a proband with a sarcoma diagnosed before forty-five years of age, a first degree relative with any cancer under forty-five years, and a first or second degree relative with any cancer under forty-five years or a sarcoma at any age.[15] In addition to breast cancer, other associated malignancies include brain tumors, adrenocortical carcinoma, and leukemia, and several less commonly seen malignancies.[14,16] Patients with similar cancer patterns that do not meet the definition of classical Li-Fraumeni Syndrome have been categorized as Li-Fraumeni-like Syndrome.[17] Approximately 70% of patients with classical Li-Fraumeni Syndrome carry *TP53* gene mutations.[16,17] Patients with Li-Fraumeni-like Syndrome exhibit a much lower frequency of *TP53* gene mutations.

Our patient, originally diagnosed with nonmetastatic osteosarcoma that later metastasized, subsequently developed an intracranial PNET with MIC2 protein expression. Central PNETs are negative for MIC2 protein, and although they look histologically identical to those arising in peripheral sites, they do not exhibit the characteristic chromosomal translocations of peripheral PNETs, which result in the fusion of the EWS gene with other Ets family transcription genes.[18] Although our molecular studies did not show a fusion gene, we searched only for 2 of the most common, EWS/FLI-1 and EWS-ERG. The possibility of a variant fusion gene cannot be excluded.[19] Peripheral-type PNET belongs to the Ewing sarcoma family of tumors, and has been reported in intracranial locations.[20] Other tumor types were excluded: neuroblastoma, which can show rosettes, is negative for MIC2 protein and strongly positive for synaptophysin; meningioma of small cell type is positive for EMA; glial tumors express GFAP and lack rosettes. Malignant lymphoma does not show rosette formation as did the present tumor. The patient does not have a significant family history of malignancy, but because of his characteristic malignancies, he may be classified as having Li-Fraumeni-like Syndrome.

Acknowledgments

We would like to thank Dr. Christine Mueller and Ms. June Peters, National Cancer Institute and Ms. Ann Carr, Westat, Inc., for their assistance in genetic counseling. This research was supported by the Intramural Research Program of the National Institutes of Health and the National Cancer Institute.

This research was supported by the Intramural Research Program of the NIH, National Cancer Institute, Center for Cancer Research and Division of Cancer Epidemiology and Genetics. The views expressed do not necessarily represent the views of the National Institutes of Health or the United States Government.

References

1. Feig SA. Second malignant neoplasms after successful treatment of childhood cancers. *Blood Cells Mol Dis*. 2001; 27(3):662–666. [PubMed: 11482881]
2. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med*. 2006; 355(15):1572–1582. [PubMed: 17035650]
3. Fraumeni, JF., Jr; Curtis, RE.; Edwards, BK., editors. Introduction. Bethesda: National Cancer Institute; 2006. p. 1-7.
4. Mertens AC, Yasui Y, Neglia JP, et al. Late mortality experience in five-year survivors of childhood and adolescent cancer: the Childhood Cancer Survivor Study. *J Clin Oncol*. 2001; 19(13):3163–3172. [PubMed: 11432882]
5. Engels, EA.; Fraumeni, JF., Jr, editors. New malignancies following cancer of the bone and soft tissue, and Kaposi sarcoma. Bethesda: National Cancer Institute; 2006. p. 313-337.
6. Paulino AC, Fowler BZ. Secondary neoplasms after radiotherapy for a childhood solid tumor. *Pediatr Hematol Oncol*. 2005; 22(2):89–101. [PubMed: 15804994]
7. Hauben EI, Arends J, Vandenbroucke JP, et al. Multiple primary malignancies in osteosarcoma patients. Incidence and predictive value of osteosarcoma subtype for cancer syndromes related with osteosarcoma. *Eur J Hum Genet*. 2003; 11(8):611–618. [PubMed: 12891382]
8. Neglia JP, Robison LL, Stovall M, et al. New primary neoplasms of the central nervous system in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *J Natl Cancer Inst*. 2006; 98(21):1528–1537. [PubMed: 17077355]
9. Caglar K, Varan A, Akyuz C, et al. Second neoplasms in pediatric patients treated for cancer: a center's 30-year experience. *J Pediatr Hematol Oncol*. 2006; 28(6):374–378. [PubMed: 16794506]
10. Bacci G, Ferrari C, Longhi A, et al. Second malignant neoplasm in patients with osteosarcoma of the extremities treated with adjuvant and neoadjuvant chemotherapy. *J Pediatr Hematol Oncol*. 2006; 28(12):774–780. [PubMed: 17164644]
11. Narod SA, Stiller C, Lenoir GM. An estimate of the heritable fraction of childhood cancer. *Br J Cancer*. 1991; 63(6):993–999. [PubMed: 2069856]
12. Wang LL, Levy ML, Lewis RA, et al. Clinical manifestations in a cohort of 41 Rothmund-Thomson syndrome patients. *American journal of medical genetics*. 2001; 102(1):11–17. [PubMed: 11471165]
13. Goto M, Miller RW, Ishikawa Y, et al. Excess of rare cancers in Werner syndrome (adult progeria). *Cancer Epidemiol Biomarkers Prev*. 1996; 5(4):239–246. [PubMed: 8722214]
14. Li FP, Fraumeni JF Jr. Soft-tissue sarcomas, breast cancer, and other neoplasms. A familial syndrome? *Ann Intern Med*. 1969; 71(4):747–752. [PubMed: 5360287]
15. Li FP, Fraumeni JF Jr, Mulvihill JJ, et al. A cancer family syndrome in twenty-four kindreds. *Cancer Res*. 1988; 48(18):5358–5362. [PubMed: 3409256]
16. Kleihues P, Schauble B, zur Hausen A, et al. Tumors associated with p53 germline mutations: a synopsis of 91 families. *Am J Pathol*. 1997; 150(1):1–13. [PubMed: 9006316]
17. Varley JM, Evans DG, Birch JM. Li-Fraumeni syndrome--a molecular and clinical review. *Br J Cancer*. 1997; 76(1):1–14. [PubMed: 9218725]
18. Ishii N, Hiraga H, Sawamura Y, et al. Alternative EWS-FLI1 fusion gene and MIC2 expression in peripheral and central primitive neuroectodermal tumors. *Neuropathology*. 2001; 21(1):40–44. [PubMed: 11304041]

19. Ladanyi M, Lewis R, Garin-Chesa P, et al. EWS rearrangement in Ewing's sarcoma and peripheral neuroectodermal tumor. Molecular detection and correlation with cytogenetic analysis and MIC2 expression. *Diagn Mol Pathol.* 1993; 2(3):141–146. [PubMed: 8287228]
20. Kazmi SA, Perry A, Pressey JG, et al. Primary Ewing sarcoma of the brain: a case report and literature review. *Diagn Mol Pathol.* 2007; 16(2):108–111. [PubMed: 17525681]

Fig. 1.

Microscopic components of humeral and cerebral tumor in the patient. **A:** Hematoxylin-eosin stain from the left humeral tumor shows spindle component with vascular stroma consistent with high-grade osteosarcoma. **B:** Hematoxylin-eosin stain shows poorly differentiated round cells with focal formation of rosettes (arrow) from the frontal cerebral mass. No osteoid is present. Tumor cells were negative for glial fibrillary protein. **C:** Immunohistochemical staining for MIC2 protein with membranous staining in the cells. Positive MIC2 stain favors peripheral type primitive neuroectodermal tumor (PNET).

Fig. 2. Post gadolinium images of the brain. **A:** Axial image. **B:** T1 post gadolinium sagittal image with fat saturation demonstrates heterogenous enhancing 5.6×4.2 cm mass in the left parasagittal frontal lobe.