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Development of Secondary Acute Myeloid Leukemia in a Pediatric Patient Concurrently Receiving Primary Therapy for Ewing Sarcoma

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Summary

Ewing sarcoma is a pediatric bone and soft tissue sarcoma that requires intensive therapy, which can cause secondary malignancies. We present a rare case of early, treatment-related AML in a pediatric patient concurrently receiving primary therapy for Ewing sarcoma. Despite AML-directed therapy, our patient died secondary to complications of hyperleukocytosis. Cytogenetic and mutation profiling of the leukemia cells revealed the DNA-topoisomerase-II-inhibitor-associated t(9;11)(p22;q23) translocation and clonal *KRAS* and *BRAF* mutations. This report highlights the importance of monitoring for treatment-related effects in cancer therapy, as well as the need for novel, less toxic approaches in Ewing sarcoma therapy.

Keywords

secondary AML; ewing sarcoma; leukapheresis; *KRAS*; *BRAF*

Ewing sarcoma is the second most common bone tumor in children. Current therapy consists of systemic chemotherapy and local control, surgery, and/or radiation. This treatment regimen is associated with the risk of secondary acute myeloid leukemia (AML). While secondary AML typically occurs after completion of the primary therapy, we present a rare case of treatment-related AML that occurred while the patient was still receiving primary therapy for Ewing sarcoma, approximately 9 months from primary diagnosis.

CASE REPORT

Our patient initially presented at 13 years of age with a right-sided chest wall mass that measured 5.4×4.4×3.8 cm³. Surgical biopsy of the mass was diagnostic for a Ewing sarcoma/primitive neuroectodermal tumor. Tumor cells were strongly positive for FLI-1 and CD99, but negative for WT-1, DC45, AE1/3, EMA and myogenin A. A next-generation-sequencing-based assay for detection of gene fusions in sarcomas (Universal-RNA-Fusion-

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Detection-Kit; ArcherDX, Boulder, CO) revealed a type-I *EWRS-FLII* fusion product (fusion of *EWRS* exon-7 with *FLII* exon-6) (Fig. 1). Metastatic work-up, including bone marrow, bone scan, and FDG-PET, was negative.

She was treated with a 5-drug (vincristine/doxorubicin/cyclophosphamide/ifosfamide/etoposide), 12-week Induction therapy on Children's Oncology Group-(COG) study AEWS1031, Regimen-A. Gross total resection of her primary tumor was obtained at the end of induction therapy and pathological examination of the mass did not reveal any viable tumor. Similarly, postsurgical imaging did not reveal any residual tumor. Postsurgical, 5-drug Consolidation therapy continued without event until cycle-9, week-17 of therapy.

While awaiting count recovery from etoposide/ifosfamide therapy, our patient experienced a 1-month delay in count recovery despite protocol-directed use of G-CSF. Approximately 5.5 weeks from her last dose of chemotherapy, she presented with a progressive cough of 2 weeks, acute fever of 102.2°F, respiratory distress, and bleeding gums. On exam she was found to have gingival hypertrophy, tachypnea with decreased breath sounds, tachycardia, hypoxia, and hypotension.

Laboratory evaluation was remarkable for hyperleukocytosis (WBC, 233,400/mm³), an elevated blast count (127,180/mm³), anemia (hemoglobin 7.3 g/dL), thrombocytopenia (platelet count 118,000/mm³), metabolic acidosis (HCO₃ 9 mEq/L, lactic acid 13.8 mEq/L, venous blood pH 7.10), tumor lysis syndrome (potassium 5.2 mEq/L, creatinine 1.2 mg/dL, uric acid 9.9 mg/dL), and coagulopathy (PT 20 s, INR 2.1, PTT 47 s, D-Dimer 5.09 µg/mL). The peripheral blood smear was consistent with AML. Following multiple fluid boluses and a dose of rasburicase (0.1 mg/kg), she had a central line placed in the operating room. She remained intubated postoperatively and underwent a bone marrow exam with aspirate and biopsy. Flow cytometry confirmed the diagnosis of M4-5 AML. The blast cells, which consisted of 90% of all of the cells, were positive for CD13, CD14, CD16, CD33, CD38, CD45, CD64, CD117, and HLA-DR. The blast cells were negative for CD15 and CD34.

Our patient was started on low-dose cytarabine (100 mg/m² IV q12), dosing per Induction-I of COG study AAML03P1. She also received two cycles of leukapheresis, which reduced her WBC to 48,200/mm³. However, her WBC rebounded to 76,700/mm³ within 10-hours of completion of the leukapheresis. Because of her rapidly increasing WBC count, ongoing metabolic acidosis, and ventilation difficulties, high-dose cytarabine (1 g/m² IV q12) was initiated on hospital day 2, with cytarabine dosing per Induction-I of COG study CCG2951. Continuous renal replacement therapy was initiated 5-hours following her first dose of high-dose cytarabine for management of fluid overload and tumor lysis.

Despite significant improvement in her WBC count (8500/mm³ nadir) and coagulopathy, our patient had progressive pulmonary disease that required high-frequency-oscillatory-ventilation (HFOV) by hospital day 3. She remained on vasopressor support and was acidotic with severe volume overload despite aggressive continuous renal replacement therapy and fluid management. Continuous electroencephalogram performed on hospital day-6 revealed diffuse cerebral dysfunction. A care conference discussion involving all of

the treating subspecialty teams and the family resulted in the decision to provide comfort care. She was subsequently taken off HFOV support and died shortly thereafter.

Bone marrow evaluation from admission revealed a cellular bone marrow (100%) with complete replacement of the marrow space with predominantly immature myeloid precursors and blasts. Cytogenetic evaluation revealed 46, XX, t(9;11)(p22;q23) and FISH studies showed a *MLL*-gene rearrangement signal pattern in 96.0% of nuclei. Institutional cancer mutation profile testing (Ion-AmpliSeqTMCancer-HotSpot-Panel-V2; Life Technologies, Carlsbad, CA) revealed mutations in *KRAS* (c.182_183delinsGC, p. Q61R) and *BRAF* (c.1799T > A, p.V600E) with allelic frequencies of 36% and 5.4%, respectively (Fig. 2). A *KRAS*-G12D mutation was also detected at a lower frequency (2.9%) in the bone marrow. FoundationOne next-generation-sequencing testing, which detects 405 cancer-related genomic alterations and 265 gene fusions, identified the same mutations and fusions identified in our institutional test. Although FoundationOne does not report quantitative clonal frequencies, the *BRAF*-V600E and *KRAS*-G12D mutations are described as subclonal, consistent with the results of our institutional test.

DISCUSSION

Ewing sarcoma is a malignant tumor of the bone and soft tissues, which most frequently occurs in teenagers and young adults. Current treatment of Ewing sarcoma includes intensive systemic and local therapies. Although this regimen results in improved overall survival, the use of radiation, high-dose-alkylators, and DNA-topoisomerase-II-inhibitors are associated with secondary malignancies. The cumulative incidence of secondary malignancies caused by Ewing sarcoma therapy is estimated to be 5% to 6% within 10 years of diagnosis. Notably, myelodysplastic syndrome (MDS) and AML comprise 60% of these secondary malignancy cases.¹⁻³

Treatment-related MDS and AML (t-MDS/AML) caused by alkylating agents (ifosfamide/cyclophosphamide) typically develops 4- to 7-years after exposure and has been linked to genetic abnormalities involving chromosomes 5 (-5/del(5q)) and 7 (-7/del(7q)). DNA-topoisomerase-II-inhibitor-associated (epipodophyllotoxin/anthracycline) t-MDS/AML usually develops 1.5 to 3 years after exposure and is associated with balanced translocations involving chromosome bands 11q23 (most common), 21q22, t(8;21) (q22q22), t(3;21), inv(16)(p13q22), t(8;16), t(15;17)(q22,12), and t(9;22).^{1,4-6} On the basis of the 11q23 translocation, we attribute the on-therapy, t-AML in our patient to etoposide and doxorubicin exposure.

Because of our patient's abnormally early presentation of secondary malignancy, the possibility of cancer predisposition through a germline mutation was explored. No *TP53* mutation was detected to support Li-Fraumeni syndrome.^{4,7} No mutation in *RB* was detected and there was no previous personal or family history of retinoblastoma.¹ No deletion of *CDKN2A* was detected.⁷ No mutations in *FANCA*, *FANCC*, *FANCD2*, *FANCE*, *FANCF*, *FANCG*, or *FANCL* were detected and our patient had no physical features suggestive of Fanconi anemia.⁴

Evaluating potential other treatment risk factors, we considered the combinatorial use of G-CSF, which has been recently associated with an increased incidence of secondary malignancies, particularly when used with high-dose-alkylator and epipodophyllotoxin chemotherapy.^{1,8} The mechanism of secondary malignancy is proposed to be the result of a stimulated blast proliferation following DNA damage to hematopoietic stem cells.^{1,8} However, because of limited evidence, and confounding treatment factors, we cannot conclude G-CSF had any direct role in the development of leukemia in our patient.

t-MDS/AML has a poor prognosis and the 5-year survival rate (23.7%) is significantly lower than that of children with AML as a first primary cancer (53.2%).^{6,9} Etoposide-related t-MDS/AML has the poorest prognosis, with a 2-year survival rate of 17.6%.^{6,9} Notably, t-MDS/AML with *RAS/BRAF* mutations is associated with a very short survival (median survival 1-month, $P=0.017$).¹⁰ We did an English language search in Ovid, Google Scholar, and PubMed using the keywords “t-AML” and “*KRAS* and *BRAF*” and found only one report of concurrent *KRAS*-13D and *BRAF*-V600E subclonal disease t-MDS/AML in a 69-year-old female who received primary therapy for small cell lung cancer, diagnosed with t-AML 11 months into her primary therapy.^{7,11} To our knowledge, no pediatric cases of t-AML with concurrent *KRAS* and *BRAF* subclonal disease, occurring while receiving primary therapy, have been described in English literature.

In summary, pediatric t-AML occurring while on therapy for a primary cancer is a rare complication. In the case of our patient, the early and aggressive disease may have been the result of the *MLL-MLLT3* gene fusion and the concurrent mutations in *KRAS* and *BRAF*. Awareness of this possible complication of therapy may help facilitate early diagnosis and immediate treatment. This case also highlights the importance of developing novel treatment regimens for Ewing sarcoma that are associated with decreased toxicity.

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FIGURE 1. Archer Fusion Analysis Jbrowse showing the *EWSR1-FLII* fusion and the breakpoint (indicated by the red line) in the chest wall mass.

FIGURE 2.

Integrated genomic view of *KRAS c.182_183delinsGC, p.Q61R* (A) and *BRAF c.1799T>A, p.V600E* (B) mutations detected in the leukemia cells by next generation sequencing. The locations of the mutations are indicated between the dashed lines.