Therapy-related mixed phenotype acute leukemia in a pediatric survivor of Ewing sarcoma with a novel RUNX1-TAF3 fusion: A case report and review of the literature

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Abstract

Increasing treatment intensity for pediatric Ewing sarcoma (ES) has improved survival, but comes with an increased incidence of secondary malignancy. Here, we describe a case of therapy-related mixed phenotype acute leukemia (t-MPAL), T-myeloid type, in a pediatric patient four years after completion of therapy for ES. Genomic evaluation revealed a novel and likely pathogenic RUNX1-TAF3 fusion. This patient did not respond to T-cell leukemia-directed therapy, and while he initially responded to myeloid leukemia-directed therapy, he never achieved complete remission and died of disease 10 months after diagnosis. Here, we present this case and review prior literature regarding t-MPAL.

Full Title: Therapy-related mixed phenotype acute leukemia in a pediatric survivor of Ewing sarcoma with a novel RUNX1-TAF3 fusion: A case report and review of the literature

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Abbreviations:

ES	Ewing Sarcoma
MPAL	Mixed phenotype acute leukemia
SMN	Secondary malignant neoplasm
AML	Acute myeloid leukemia
WHO	World Health Organization
MDS	Myelodysplastic syndrome
ALL	Acute lymphoblastic leukemia
t-MPAL	Therapy-related mixed phenotype acute leukemia
MRD	Minimal residual disease
COG	Children's Oncology Group
CR	Complete Remission
HSCT	Hematopoeitic stem cell transplant

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Abstract:

Increasing treatment intensity for pediatric Ewing sarcoma (ES) has improved survival, but comes with an increased incidence of secondary malignancy. Here, we describe a case of therapy-related mixed phenotype acute leukemia (t-MPAL), T-myeloid type, in a pediatric patient four years after completion of therapy for ES. Genomic evaluation revealed a novel and likely pathogenic RUNX1-TAF3 fusion. This patient did not respond to T-cell leukemia-directed therapy, and while he initially responded to myeloid leukemia-directed therapy, he never achieved complete remission and died of disease 10 months after diagnosis. Here, we present this case and review prior literature regarding t-MPAL.

Introduction:

Modern treatment modalities have improved survival for childhood cancer substantially. In particular, Ewing sarcoma (ES) has seen a dramatic improvement in survival, mostly owing to aggressive local and systemic therapy.[1] Unfortunately, due to exposure to genotoxic therapy including topoisomerase II inhibitors, alkylating agents, anthracyclines and radiation, treatment for ES carries a significant risk of secondary malignant neoplasms (SMNs), with therapy-related AML/MDS being the most common.[2,3] Overall survival after diagnosis of secondary leukemia in children ranges from 20-40%, though some have reported more optimistic outcomes, especially when patients are treated with allogeneic stem cell transplantation.[4–11] Mixed phenotype acute leukemia (MPAL), defined by the World Health Organization (WHO) as acute leukemia with immunophenotypic expression of both lymphoid (T or B) and myeloid cell markers, is a rare entity accounting for 3-5% of *de novo*pediatric acute leukemias.[12,13] Outcomes of *de novo* pediatric MPAL are similar to those of *de novo* AML, though significantly worse than those of ALL. There is controversy over standard MPAL treatment, with many providers favoring ALL-type therapy.[12] Therapy-related MPAL (t-MPAL) is rare and, to our knowledge has been reported only once in a child, who harbored a B-myeloid variant.[14] Here, we report a case of t-MPAL, T-myeloid type, in a childhood survivor of Ewing sarcoma.

Case Presentation:

A two-year-old male was diagnosed with localized Ewing sarcoma of the left scapula and was enrolled on the Children's Oncology Group (COG) clinical trial AEWS1031. He received systemic vincristine, doxorubicin, cyclophosphamide, etoposide and ifosfamide as well as 5580cGy external beam radiation to the left scapula. His clinical course was complicated by severe veno-occlusive disease/sinusoidal obstruction syndrome, respiratory failure, disseminated varicella and fungal infections, pancreatitis, and cardiomyopathy. He fortunately recovered from these complications and was in complete remission by the end of therapy.

He was subsequently treated for late effects of therapy including developmental delay, functional limitations with mobility, and transfusion related-iron overload, for which he was briefly phlebotomized.

Four years after completion of therapy for ES, routine labs showed progressive pancytopenia prompting further evaluation. Bone marrow morphology showed hypercellularity with myelofibrosis; flow cytometry showed two abnormal blast populations, both with predominantly T-cell marker expression and minimal myeloid differentiation: cytoplasmic CD3 (majority subset), CD7 (bright), CD33 (uniform), CD34 (variable), CD38, CD45, CD56 (small subset), CCD71, CD117 (variable), CD123 (variable), HLA-DR. There was no significant expression of CD2, surface CD3, CD4, CD5, CD8, CD10, CD14, CD15, CD16, CD19, CD20, CD64, cytoplasmic CD79a, cytoplasmic MPO or surface light chains.

Cytogenetic analysis revealed a clonal population with loss of chromosome 6, gain of chromosome 13, and a ring chromosome in 60% of cells. A cancer genetics panel (UCSF500) showed a pathogenic *NRAS*mutation and a novel RUNX1-TAF3 structural variant, predicted to result in a functional fusion gene product and considered likely pathogenic. Germline testing showed no alterations in cancer-related genes. Based on these data, the patient was diagnosed with t-MPAL, T-myeloid type.

A summary of the patient's treatment course is presented in Table 1. Briefly, per current guidelines for *de novo* pediatric MPAL[15], he received ALL-type induction therapy without a response. End of induction marrow evaluation showed progression of disease as well as a third clonal population with 17% of cells expressing monosomy 7. He was re-induced with AML-type therapy and had a significant response, with minimal residual disease (MRD) of 0.09% by flow cytometry. Subsequent attempts were made to achieve complete remission (CR) with the goal to proceed with allogeneic hematopoietic stem cell transplant (HSCT), however these attempts were unsuccessful. Due to prior cardiotoxicity, he was not a candidate for additional anthracycline therapy. The patient died of disease progression 10 months after diagnosis of t-MPAL at age 8.

Discussion:

Secondary malignant neoplasms (SMNs) are a rare but potentially devastating complication for survivors of childhood cancer. Therapy-related AML/MDS is the most common SMN and it remains difficult to cure despite use of aggressive therapies, often including HSCT. With Ewing sarcoma in particular, prior studies have shown that survivors of ES have a significantly increased risk of secondary AML. One large cancer registry study reported that the standardized incidence ratio (SIR; observed to expected ratios based on age- and sex-specific incidence in the general population) for AML after ES was 71.17.[16] Although therapy-related hematologic malignancies in survivors of childhood cancer have been well described, secondary, or therapy-related MPAL is rare.

We have identified eight prior published cases of t-MPAL, four B-myeloid and four T-myeloid, and summarized major clinical features in Table 2. Cases had variable exposures for treatments of different primary diseases and varied immunophenotypic and cytogenetic characteristics. Most patients initially received AML-directed therapy. Only two of the nine patients reviewed here (including the present case) were alive at the time of case report: one was diagnosed with a Philadelphia-chromosome positive t-MPAL and was treated with an imatinib-containing regimen; the other underwent HSCT after achieving CR with ALL-type induction therapy. As is the case with *de novo*pediatric MPAL, recurrent chromosomal abnormalities have not been identified.

We present the first published case of t-MPAL of the T-myeloid type in a pediatric patient. This lineage assignment is essential because it helps determine management. Diagnosis of MPAL, however, is evolving and is often not straightforward. In this case, the immunophenotype, with strong expression of cytoplasmic CD3 was highly suggestive of T-cell leukemia. Blasts also expressed myeloid markers, CD33 and CD117, thus it may be argued that these myeloid markers represented aberrant expression rather than defining the lineage. Although our patient did not meet strict WHO 2016 criteria for myeloid leukemia (requires either MPO expression or 2 markers of monocytic differentiation including NSE, CD11c, CD14, CD64 or lysozyme), a number of supporting factors validate the diagnosis of T-myeloid MPAL. The first of these is

history of treatment for ES, which carries a notable increased risk for AML as mentioned above. Second, this patient responded to myeloid, but not T-lymphoid therapy. Third, a cancer genetics panel (UCSF500) identified an activating mutation in *NRAS* , which is commonly found in*de novo* MPAL and AML. Lastly, the leukemia developed five years after alkylator exposure and included a clonal population with monosomy 7. Alkylating agents have been associated with development of AML 5-7 years after exposure, frequently with loss or deletion of chromosomes 5 or 7. [17]

We also identified a novel fusion of RUNX1 with TAF3. *RUNX1* , on chromosome 21, is a member of the core-binding factor family of transcription factors and is a critical regulator of hematopoiesis.[18] Mutations in *RUNX1* are commonly thought to be drivers of leukemogenesis. Further, structural variants including fusions of RUNX1 are very common in pediatric AML.[19] Notably, *NRAS* mutations have been seen in a third of AML patients with certain RUNX1 rearrangements.[18] *TATA-box binding protein associated factor 3* , *TAF3,* on chromosome 10, has been documented in structural variants involving *NUP* family genes, but not as a fusion partner with RUNX1. This novel fusion places exons 1-7 of*RUNX1* in frame with exons 3-7 of *TAF3* , which is predicted to result in a pathogenic gene product.

This case, the first reported therapy-related T-myeloid MPAL in a pediatric patient, represents the growing importance of molecular diagnostics not only in predicting the behavior of hematologic malignancies, but potentially also in choosing appropriate therapy.

Disclosure of conflicts of interest: None

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