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Intracardiac low-grade sarcoma following treatment for Ewing sarcoma

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Abstract

A 16 year old young man was diagnosed with Ewing sarcoma of the ribcage with pulmonary metastases. Six months after completion of scheduled therapy he was found to have a new intracardiac mass, presumed recurrent Ewing sarcoma. *EWSR1* fusion was not detected via droplet digital PCR from blood plasma. After no improvement with salvage chemotherapy, he underwent surgical resection which identified a low-grade spindle cell sarcoma. Despite the near synchronous presentation of two unrelated sarcomas, extensive genomic analyses did not reveal any unifying somatic or germline mutations nor any apparent cancer predisposition. This case also highlights the potential role of utilizing plasma cell-free DNA for diagnosing tumors in locations where biopsy confers high morbidity.

Keywords

Ewing sarcoma; Cardiac sarcoma; Low grade sarcoma; Cell-free DNA; Genomics

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Introduction

Ewing sarcoma (ES) is an aggressive embryonal malignancy which presents in soft tissue or bone. [1] Metastases occur in 20-25% of patients, the majority of which are located in the lungs, bone, or bone marrow. [2] Here, we present an adolescent male with ES of the left posterior rib with multiple pulmonary metastases. He was found to have a new FDG-avid intracardiac mass 6 months following completion of planned initial therapy on routine radiographic surveillance. While an atypical location for an ES relapse, intracardiac ES cases have been reported both at diagnosis and relapse. [3–7] Intracardiac masses give rise to diagnostic, therapeutic, and management challenges. This case illustrates how new molecular technologies may provide some solutions to these challenges.

Case Report

Our Caucasian male patient presented at age 16 to his pediatrician with a painless upper back mass which was biopsied and identified as a small round blue cell tumor (Figure 1). Cytogenetic evaluation identified an *EWSR1* rearrangement and confirmed a diagnosis of ES. Staging demonstrated bilateral sub-centimeter pulmonary metastases but no evidence of extrapulmonary disease, which notably comprised multiple cross sectional modalities with fields including his heart. He was treated on a Memorial Sloan Kettering Cancer Center trial for metastatic ES (NCT01864109), which includes 4 cycles of cyclophosphamide (4.2 mg/m^2/cycle), doxorubicin (75 mg/m^2/cycle), and vincristine (2 mg/m^2/cycle), 3 cycles of ifosphamide (14,000 mg/m^2/cycle) and etoposide (500 mg/m^2/cycle), as well as 10 cycles of irinotecan (200 mg/m^2/cycle) and temozolomide (500 mg/m^2/cycle).

Six months after the completion of his scheduled therapy, a new FDG-avid nodule within the right ventricle of his heart was identified on a surveillance PET scan (Figure 2 A,B). Although rare, intracardiac metastases have been described in ES. Given the significant surgical risks associated with a biopsy or resection in this location, a decision was made to administer salvage chemotherapy with cyclophosphamide and topotecan for presumed relapsed disease. [8] Following two cycles of salvage therapy, no significant change in size or FDG-avidity was demonstrated. Given the lack of response, the patient then underwent surgical resection of the intracardiac mass, which identified a 3 cm low-grade spindle cell sarcoma with negative margins (Figure 2C). *EWSR1* fusion testing was negative by both FISH and anchored multiplex PCR (Archer FusionPlex). Testing was negative for *MDM2* and *PDGFRA* amplification indicating it was not an intimal sarcoma. [9] Finally, we profiled both his original ES biopsy specimen and low-grade intracardiac tumor on MSK-IMPACT, a 410 gene hybrid-capture based targeted next generation sequencing platform. [10] An *EWSR1-FLI1* fusion was identified on the original ES tumor biopsy, while the intracardiac tumor revealed two silent somatic mutations, an intronic mutation of *MRE11A* and a synonymous mutation of *AMER1.*

After his first three cycles of chemotherapy, the patient was enrolled on an ongoing study evaluating the utility of identifying genomic *EWSR1* fusions from plasma-derived DNA as a potential biomarker for subclinical disease. Multiple plasma samples were collected after the

identification of the intracardiac mass, all of which were negative for the identification of an *EWSR1* fusion by droplet digital PCR.

Although ES has not been associated with classic tumor susceptibility syndromes, recent literature demonstrates that germline predispositions are more common than previously believed. [11, 12] A targeted germline evaluation of 76 genes with known associations with cancer development did not reveal any constitutional mutations. Furthermore, an additional extensive interrogation of germline *TP53* mutations was also negative. This included the bidirectional sequencing of splice junctions and corresponding coding regions (exons 2-11) along with deletion and duplication analysis to identify larger rearrangements. Given the limited differential for a cardiac tumor, notably, no mutations or copy number alterations in the *TSC1* or *TSC2* genes were detected and the young man did not exhibit any stigmata of tuberous sclerosis.

As of this submission date, the patient is 15 months post completion of therapy for his ES, excluding his two salvage cycles of chemotherapy. He does have a right bundle branch block, which was an expected result of the tumor location, but otherwise no impaired cardiac function.

Discussion

We report a case of a young Caucasian man with ES of the ribcage who was found to have a low-grade intracardiac sarcoma 6 months after completion of therapy. Despite extensive testing of somatic and germline mutations, we did not identify any consistent mutations which might indicate a common etiology of these two sarcomas. The fact that they both revealed distinct somatic mutations provides further evidence that the tumors are unlikely to be related. However, occult constitutional mutations or mosaicism cannot be excluded. Ultimately, despite a negative targeted evaluation of germline variants with known associations with cancer, it is possible that an uninterrogated gene aberration is responsible for the development of multiple malignancies in this patient.

At this point, there are no known underlying genetic predispositions which are specifically associated with ES. [11] However, the incidence of ES is nine times greater in individuals of Caucasian ancestry compared with African Americans, suggesting that there is likely a heritable factor which predisposes Caucasian patients but has yet to be defined. [13] Recent evidence has implicated GGAA-microsatellite polymorphisms in *NR0B1* as a possible etiology for this racial disparity. [14, 15]

It is possible but unlikely that this subsequent intracardiac sarcoma was treatment related. The patient received cardiac sparing radiation, and thus the dose to the heart was estimated to be quite low, approximately 10 Gy spread over 25 fractions. In a study of 266 survivors of ES, no secondary sarcomas developed in patients who had received less than 48 Gy and the shortest latency from the end of therapy to a second malignancy was 3.5 years with a median of 7.6 years, much longer than the latency in our patient. [16]

The detection of genomic fusion products by blood plasma digital droplet PCR is a promising biomarker in ES but is not yet clinically actionable. [17–18] This case highlights the

potential utility of circulating tumor DNA as a blood based biomarker for ES, particularly in situations where biopsy confers significant morbidity. Our group has recently demonstrated that EWSR1 fusions can be detected via blood droplet digital PCR in 11/11 ES patients, 7 of which were able to be detected at relapse. (Shukla N, personal communication) Ongoing studies are underway to ascertain the clinical utility of cell-free DNA in ES.

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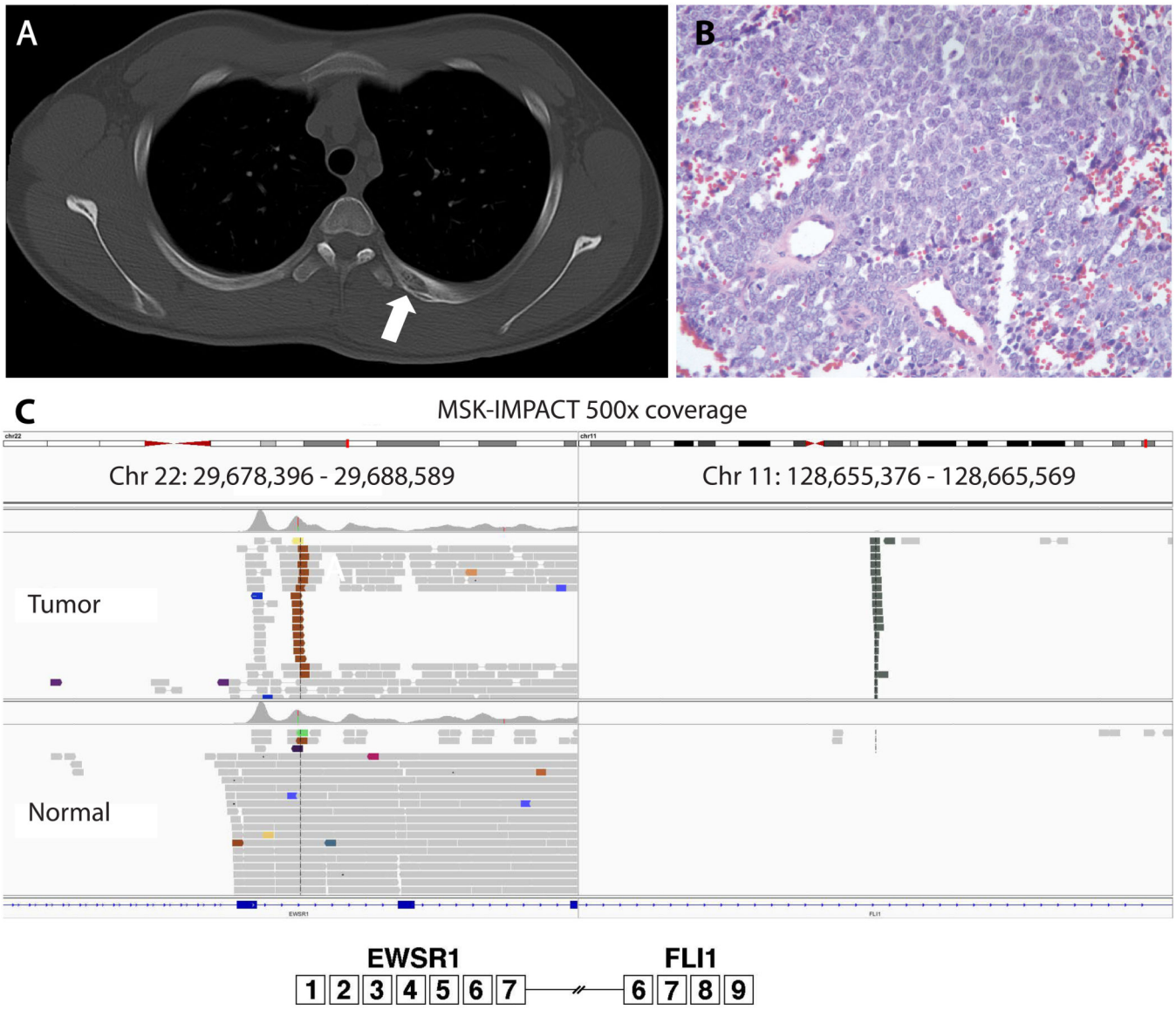

Figure 1. Key imaging and pathology results from the Ewing sarcoma

A: Axial CT scan revealed an expansile lytic lesion with periosteal reaction involving the left posterior fourth rib (arrow); B: H&E stain demonstrates a small round blue cell tumor; C: MSK-IMPACT sequencing reveals the precise coordinates of our patient's *EWSR1-FLI1* rearrangement. Note that this sequencing result had 500x coverage with no additional mutations identified.

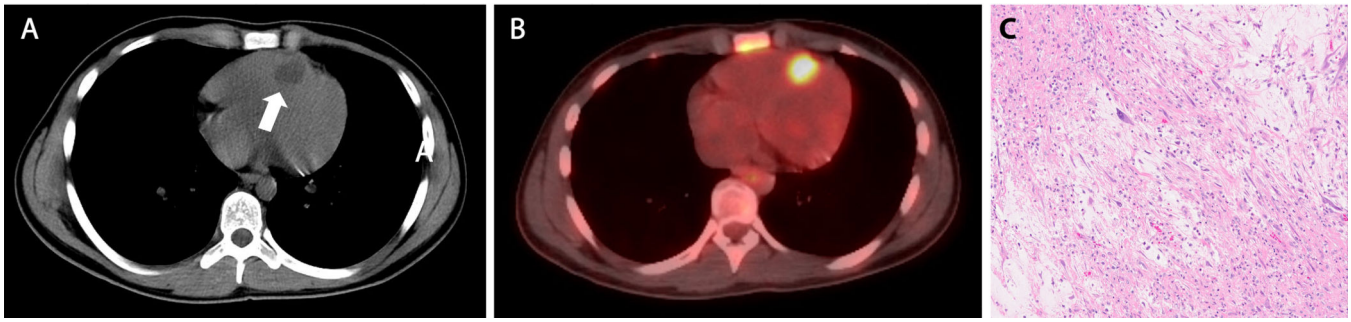

Figure 2. Key imaging and pathology findings from the low-grade intracardiac sarcoma

A: Axial noncontrast enhanced CT of the chest revealed a hypodense nodule at the apex of the right ventricle abutting the intraventricular septum (arrow); B: This lesion was FDG-avid on PET scan; C: Low-grade myxoid spindle cell neoplasm composed of atypical spindle cells with focal nuclear pleomorphism in a myxoid background is apparent on H&E stain.