Aggressive Myoepithelial Carcinoma With *EWSR1-POU5F1* Fusion Highly Responsive to Ewing Sarcoma Combination Chemotherapy

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Myoepithelial carcinoma is a rare malignancy that arises mainly from the salivary glands, but also from soft tissue, skin, bone, and visceral organs.[1-3] It is considered to be relatively chemoresistant, with no standard therapy reported within the metastatic setting.[4-6] EWS RNA-binding protein 1 (*EWSR1*) gene rearrangements are present in approximately 82% of myoepithelial tumors arising from soft tissue, bone, and visceral locations,[7] as well as in approximately 39% of clear cell myoepithelial carcinomas arising from the salivary glands.[8] POU class 5 homeobox 1 (*POU5F1*) is the fusion partner of *EWSR1* in approximately 28% of *EWSR1* rearrangement–positive myoepithelial tumors arising from soft tissue, bone, and visceral locations, with a predilection toward a more malignant phenotype.[7] *EWSR1* rearrangement is a pathognomonic feature of Ewing sarcoma (albeit with different fusion partners: Fli-1 proto-oncogene, ETS transcription factor [*FLI1*] in approximately 90% of cases and ETS transcription factor ERG [*ERG*] in approximately 10% cases).[9] This article describes a case of metastatic, bulky, high-grade, rapidly progressive myoepithelial carcinoma with *EWSR1-POU5F1* fusion originating from the left kidney that demonstrated a dramatic, deep response within 2 cycles of a combination chemotherapy regimen used to treat patients with Ewing sarcoma (vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide [VDC/IE]), with an ongoing sustained response of >10 months.

A 21-year-old African American man with a history of depression and anxiety presented to the outpatient clinic with worsening abdominal and back pain, loss of appetite, easy fatiguability, and a 25- to 30- pound weight loss over the preceding 3 to 4 months. Physical examination revealed cachexia and a large abdominal mass noted predominantly in the left upper and lower quadrants. Basic laboratory studies revealed mild normocytic anemia (hemoglobin of 11 g/dL), normal renal and hepatic function, and a high lactate dehydrogenase level (LDH) of 1691 U/L. A computed tomography (CT) scan of the abdomen and pelvis with intravenous contrast revealed a very large (17 cm) mass arising from the left kidney, crossing the midline, and extending into the porta hepatis (Fig. 1). The bulky mass and associated extensive mesenteric and retroperitoneal lymphadenopathy caused external compression of the aorta and its branches, and the inferior vena cava. The left renal artery was markedly narrowed and the left renal vein was occluded. The surrounding organs—pancreas, stomach, and spleen—were compressed. There were multiple liver lesions consistent with systemic metastatic disease. A CT scan of the chest was relatively unremarkable with no definite metastatic disease noted. Considering the renal origin of the bulky primary tumor in this young African American man, renal medullary carcinoma ranked high in the differential diagnosis. However, hemoglobin electrophoresis did not reveal sickle cell trait, a hallmark of renal medullary carcinoma. CT-guided biopsy of the large mass then revealed a poorly differentiated malignancy with a histopathologic diagnosis of high-grade myoepithelial carcinoma with *EWSR1-POU5F1* fusion as detected by fluorescence in situ hybridization. The presence of an *EWSR1-POU5F1* fusion and cytokeratin expression in the poorly differentiated malignancy best fit with a diagnosis of high-grade myoepithelial carcinoma. No reportable genomic alterations were detected using genomic testing. There were 4 variants of unknown significance noted: MER proto-oncogene, tyrosine kinase (*MERTK*)

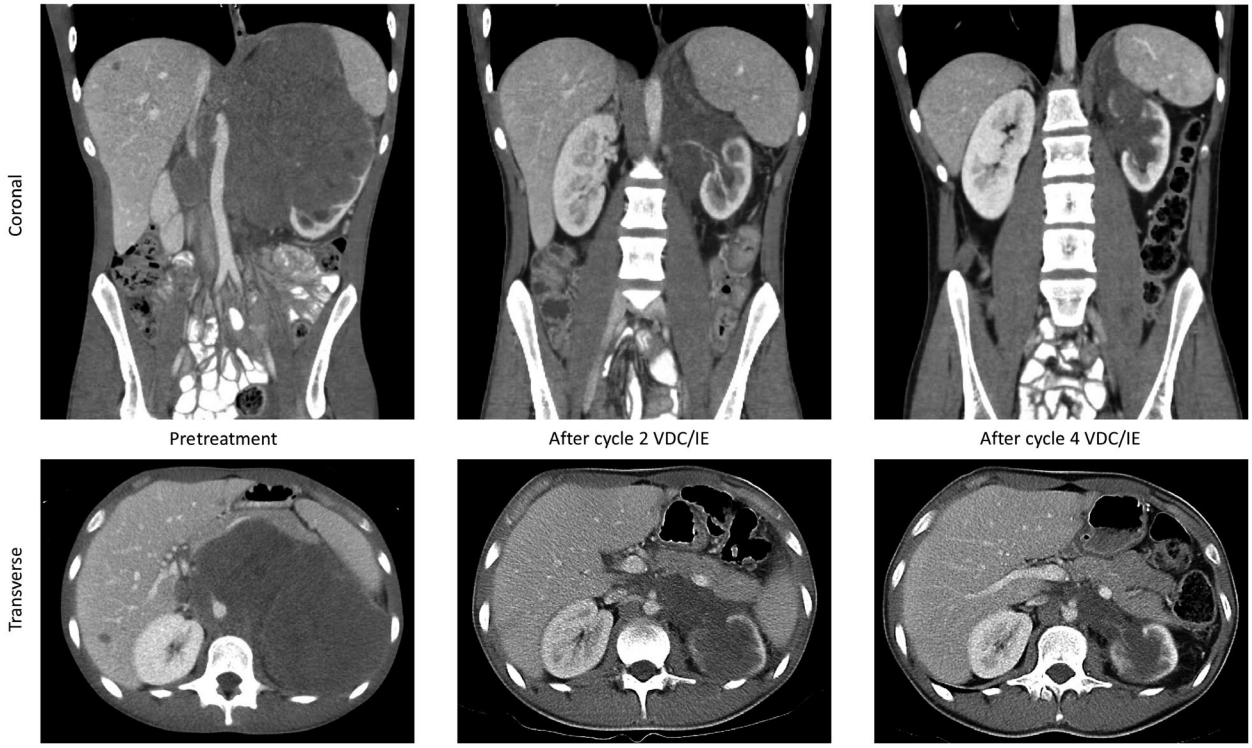

Figure 1. Coronal and transverse sections of computed tomography scans of the abdomen and pelvis with intravenous contrast (pretreatment, after cycle 2, and after cycle 4) demonstrating a deep response to chemotherapy with vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide (VDC/IE).

(R421Q); polymerase delta 1 (*POLD1*) (D679E); ring finger protein 43 (*RNF43*) (V217M); and smoothened, frizzled class receptor (*SMO*) (E224D). The tumor was microsatellite stable and the tumor mutational burden was low (0 mutations per megabase).

During the workup, the patient's clinical status deteriorated precipitously (with increasing pain and requirements for opiates, worsening oral intake, progressive cachexia, and debilitating fatigue), suggestive of a rapidly progressing malignancy. Once the diagnosis of high-grade myoepithelial carcinoma with *EWSR1-POU5F1* fusion was established, and much before the absence of targetable genomic alterations was reported (Foundation Medicine), a decision was made to initiate the Ewing sarcoma VDC/IE combination chemotherapy regimen. The choice of VDC/IE was based primarily on the partly shared genetic pathology with Ewing sarcoma, involving *EWSR1* rearrangement (albeit with a different partner in *POU5F1* instead of *FLI1* or *ERG*). The *POU5F1* gene encodes a transcription factor that plays a key role in embryonic development and stem cell pluripotency, with aberrant expression resulting in malignancy (as with myoepithelial carcinoma *EWSR1-POU5F1* fusion). The *FLI1* gene also encodes a transcription factor that orchestrates multiple oncogenic pathways when aberrantly expressed (as with *EWSR1-FLI1* fusion in Ewing sarcoma). The *EWSR1* amino-terminal domain has a strong transactivation domain, and its promoter is activated ubiquitously, thus leading to uncontrolled high expression of the resulting fusion genes.[9,10] Put together, the genetic similarity between myoepithelial carcinoma with *EWSR1-POU5F1* fusion and Ewing sarcoma with *EWSR1-FLI1* fusion was an important consideration in choosing the VDC/IE regimen for this patient.

Another consideration was the hope that the rapidly progressing nature of the malignancy had conferred some chemosensitivity, and that a combination of a microtubule-destabilizing agent (vincristine), alkylating agents (cyclophosphamide and ifosfamide), an anthracycline (doxorubicin), and a topoisomerase II inhibitor (etoposide) would use different mechanisms of chemotherapeutic action simultaneously against the life-threatening disease bulk.

The patient received the first cycle of the regimen (VDC) as an inpatient so he could be closely monitored for tumor lysis and tolerance, starting the day after he received the histopathologic diagnosis. He had a remarkable clinical response to the first cycle, with a significant reduction in pain and requirements for opiates, an improvement in appetite and energy levels, and a drop in his LDH level from 2140 U/L to 250 U/L within 3 weeks. A follow-up CT scan

after the second cycle (IE) demonstrated a marked reduction (approximately 80%) in the overall tumor burden with a significant improvement in compression of the surrounding vessels and organs (Fig. 1). After 3 cycles, the patient was asymptomatic from his cancer, did not require any pain medication, and had gained 10 pounds. Imaging performed after the fourth cycle demonstrated a continued response to treatment (Fig. 1) with shrinking liver lesions noted. At the time of last follow-up, >10 months after the initiation of treatment, the patient continued to be fully asymptomatic, had regained most of the weight lost (approximately 25 pounds), had his hemoglobin increase to 13.8 g/dL, and his LDH level decrease to 150 U/L. The most recent CT scan performed (>10 months since the initiation of treatment) demonstrated near complete resolution of all but 2 liver lesions (the 2 lesions measuring only 0.5 cm each), and a further reduction of the primary tumor. At the time of last follow-up, the patient continued to receive VC/IE. The treatment course has required dose reductions (particularly with IE) and several delays for CTCAE (Common Terminology Criteria for Adverse Events) grade 3 to 4 neutropenia (which can be a potential indicator of treatment response) and grade 1 to 2 nephrotoxicity (his glomerular filtration rate improved to 77 mL/minute/body surface area). However, the course largely has been well tolerated in terms of symptoms. The patient had not experienced a single episode of febrile neutropenia at the time of last follow-up. Occasional grade 1 to 2 nausea has been controlled with conventional antiemetics as needed. It should be noted that the planned regimen was VDC/IE as given in the AEWS1031 study regimen A (every 2 weeks for a total of 17 cycles, 6 of which are induction and 11 of which are consolidation). However, given the several delays for grade 3 to 4 neutropenia, a majority of cycles were administered at intervals of ≥3 weeks.

At the start of treatment, the goal was palliative, considering not just the metastatic disease but also the generally chemoresistant nature of the malignancy, the degree of tumor burden, and local organ and vessel infiltration and/or compression. However, given the remarkable response to the VDC/IE chemotherapy regimen, the goal now is to maintain a long-term remission. Surgical resection of the primary tumor may be a consideration, particularly if there is no significant remnant vessel and/or organ infiltration after consolidation therapy with VC/IE. Ablation of the remnant oligometastatic lesions also may be considered.

To my knowledge, this is the first report of a rapid and deep response using a systemic therapy regimen in a patient with myoepithelial carcinoma with *EWSR1-POU5F1* fusion. The VDC/IE regimen holds promise in this setting, and deserves further exploration. In addition, future studies with genome-wide chromatin immunoprecipitation sequencing analyses could help to determine the degree of overlap between the *EWSR1-POU5F1* target gene repertoire in patients with myoepithelial carcinoma and that of *EWSR1-FLI1* in patients with Ewing sarcoma.

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CONFLICT OF INTEREST DISCLOSURES

The author declares no conflict of interest.

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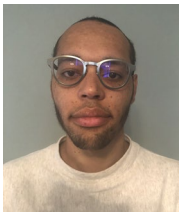
Patient



Julian Hargrove
Patient, Julian Hargrove, provided permission and requested that his name and headshot be included with the article.