Durable Response to PD-1 Blockade in a Patient With Metastatic Pancreatic Undifferentiated Carcinoma With Osteoclast-Like Giant Cells

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ABSTRACT

Undifferentiated carcinoma with osteoclast-like giant cells (UCOGC) of the pancreas is a rare and potentially aggressive variant of pancreatic ductal adenocarcinoma. Data on this disease are sparse, and despite genetic similarities to pancreatic ductal adenocarcinoma, UCOGC clinical outcomes can be markedly different. We report on a female patient aged 62 years who presented with UCOGC with pulmonary metastases initially treated with 2 lines of cytotoxic chemotherapy. After rapid disease progression with both cytotoxic treatments, the patient's tissue was sent for next-generation sequencing, which revealed a high tumor mutation burden (32 mutations per megabase), as well as somatic mutations in *BRAF*, *NF1*, *PIK3CA*, *CDKN2A*, *TERT*, and *TP53*. Pancreatic cancers have previously demonstrated suboptimal responses to immunotherapeutic approaches. However, given the high tumor mutation burden and distinctiveness of the tumor class, the patient began third-line pembrolizumab monotherapy after palliative radiation to the rapidly progressing and painful abdominal mass from her primary tumor. She had a marked response in her primary UCOGC tumor and metastatic sites, and she remains on pembrolizumab monotherapy with ongoing response after 32 months of therapy. Recent evidence showing significant PD-L1 enrichment on neoplastic cells of undifferentiated carcinomas (including UCOGC) may indicate a role for immunotherapeutic approaches in these patients. Rare cancers such as UCOGC and other undifferentiated carcinomas may benefit from next-generation sequencing to inform treatment decisions when standards of care are absent, as in this report.

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Background

Undifferentiated carcinoma with osteoclast-like giant cells (UCOGC) of the pancreas is a rare pancreatic neoplasm, constituting an estimated 1.4% of pancreatic cancer diagnoses.¹ UCOGC is a clinically distinct variant of pancreatic ductal adenocarcinoma (PDAC).² UCOGC is also cytologically distinct from PDAC because of the presence of nonneoplastic osteoclast-like giant cells, which contain >20 nuclei and mimic the giant cell tumors often found in bone and the commonly present neoplastic, pleomorphic mononuclear giant cells and histiocytoid or spindle cells.^{3,4} Furthermore, it is common for many UCOGCs to have a mixed histologic component of PDAC. Although it has strong genetic similarities to PDAC,² UCOGC can have distinct clinical outcomes requiring additional treatment considerations.

Much of the published UCOGC literature exists in case reports and small case series, making prognostication difficult. Commonly cited data suggest that UCOGC neoplasms may have a poorer prognosis than PDAC.⁵ However, the 2 largest case series to date paint a more complex picture. Muraki et al¹ found that patients with UCOGC were typically younger when diagnosed (mean age, 57.9 vs 65.0 years; $P=.0059$) and that overall survival (OS) was significantly longer compared with patients with conventional, poorly differentiated PDAC. Further, Reid et al⁶ showed that patients with UCOGC found on fine-needle aspiration before resection had poor survival, similar to those with conventional PDAC. However, for those who did not undergo fine-needle aspiration before resection and were found to have UCOGC incidentally, outcomes seemed better than expected. The authors noted that selection bias, perhaps due to patient symptoms requiring additional diagnostic procedures, may help explain their findings. In our experience, patients with UCOGC typically have poor clinical outcomes.

The preferred treatment for localized UCOGC is surgical resection when feasible, as with PDAC. This modality has led to good clinical responses in multiple

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instances,^{7,8} with some patients going on to have long-term OS postresection (19–84 months). In other patients, adjuvant chemotherapy and radiation therapy (RT) have been added to surgery, and such efforts have also shown a wide range of survival for patients with UCOGC (19–72 months).^{9,10} In the metastatic setting, no prospective data are available to support any particular systemic therapy.

In this report, we present a patient with chemorefractory metastatic UCOGC of the pancreas with a high tumor mutation burden (TMB) identified during next-generation sequencing (NGS). Third-line pembrolizumab monotherapy markedly reduced the primary pancreatic tumor and metastases in the lung and brain. Despite recent clinical trial data demonstrating poor responses to pembrolizumab in standard PDAC,¹¹ we hypothesize that the differing biology of the undifferentiated carcinoma tumor class may have allowed for such a durable response.

Case Report

An African American female patient aged 62 years with a history of asthma and a 24 pack-year smoking history presented with worsening right upper quadrant abdominal and back pain. Her family medical history included a father who died of lung cancer, a mother who died of Alzheimer disease and stroke, and a brother and sister with lung cancer who were both smokers. Chest imaging of the patient revealed a 3.7 × 2.2-cm right upper lobe pleural-based mass concerning for malignancy. After referral to thoracic surgery, PET/CT results showed avidity in the right upper lobe lesion and an avid ill-defined soft tissue density in the left upper quadrant of the abdomen measuring 4.7 × 3.9 cm (Figure 1). A CT-guided biopsy of the lung lesion revealed undifferentiated carcinoma with spindle cell malignant neoplasm with osteoclast-like giant cells consistent with UCOGC (Figure 2A, B). A dedicated abdominal CT found an enlarging exophytic 4.9-cm pancreatic tail mass. Subsequent percutaneous biopsy of the pancreatic mass was consistent with malignant spindle cell neoplasm, most consistent with UCOGC (Figure 2C). Given the specimen's morphologic similarity to the lung biopsy, it was determined that the pancreatic mass likely represented the primary disease site and that the lung mass was a metastasis.

The patient began palliative first-line chemotherapy with 5-fluorouracil, oxaliplatin, and leucovorin, with a plan to escalate to 5-fluorouracil, oxaliplatin, irinotecan, and leucovorin as tolerated. After 4 doses of 5-fluorouracil/oxaliplatin/leucovorin with intermittent treatment delays related to neutropenia and *Clostridioides difficile* infection, CT imaging revealed substantial progression of the pancreatic mass, now measuring 13.0 × 8.5 cm. The patient was then transitioned to second-line gemcitabine + nab-paclitaxel. This course was complicated by thrombocytopenia, requiring dose reductions. Due to concern for early progression after a large and expanding

Figure 1. Initial fused coronal PET/CT images showing a large, FDG-avid pancreatic tail primary tumor and lung metastasis.

abdominal mass was found extending from the left upper quadrant to almost the right lower quadrant of the abdomen, imaging was performed at 6 weeks, which again revealed substantial disease progression; the pancreatic mass now measured 21.6 × 17.1 cm (Figure 3A). The large abdominal mass was causing organ compression and pain, reducing the patient's ability to eat. She was referred for palliative RT to mitigate her symptom burden due to mass effect. Given limited data regarding the efficacy of RT in UCOGC histology, but due to the presence of spindle cell features, her radiation oncologist opted for treatment as for sarcoma, which favors aggressive palliative dosing via intensity-modulated RT (IMRT).

While the patient was undergoing IMRT, tissue from her lung metastasis was sent for NGS (FoundationOne, Foundation Medicine), which revealed alterations to the *BRAF* oncogene and the tumor suppressor genes *NF1*, *PIK3A*, *CDKN2A*, *TERT* promoter, and *TP53*. The tumor was microsatellite-stable with a high TMB (32 mutations per megabase [mut/Mb]). The patient completed IMRT (3,600 cGy in 12 fractions), which provided some symptom relief. Given the tumor's chemorefractory nature and high TMB, third-line pembrolizumab at 200 mg every 3 weeks was initiated; it had previously shown efficacy in other cancers with a high TMB.^{12,13} Routine CT imaging after 3 doses of pembrolizumab showed a decrease in the main pancreatic mass and the right upper-lobe pulmonary

Figure 2. Histologic confirmation of UCOGC: (A) lung biopsy (H&E, original magnification $\times 100$), (B) lung biopsy (H&E, original magnification $\times 400$), (C) pancreas biopsy (H&E, original magnification $\times 200$), (D) pancreas biopsy touch preparation (Giemsa stain, original magnification $\times 400$). Abbreviations: H&E, hematoxylin-eosin; UCOGC, undifferentiated carcinoma with osteoclast-like giant cells.

metastasis. At the time of pembrolizumab initiation, the patient was unable to eat because of her large tumor bulk and she had transfusion-dependent anemia; after treatment initiation, her oral intake quickly improved and her anemia normalized within 5 months.

During cycle 6, the patient developed headaches and auditory hallucinations. A brain MRI scan revealed a 3.3×3.0 -cm right posterior temporal mass of unknown age because no prior brain imaging had been performed. The mass was considered a likely metastasis given the aggressive nature of her cancer, and neither biopsy nor resection for pathologic confirmation were considered in the patient's best interest. While continuing pembrolizumab, the patient underwent palliative stereotactic radiosurgery to the brain lesion (3,000 cGy in 5 fractions), which resulted in a reduction of the lesion on MRI and resolution of her reported neurologic symptoms. She subsequently

developed radiation-induced necrosis, which was managed successfully with bevacizumab, and her brain metastasis has not recurred at the time of writing.

The patient continued pembrolizumab cycles 8 through 19 with continued reduction of the pancreatic primary and brain metastasis and complete resolution of the pulmonary metastasis biopsied at diagnosis. Cycles 20 through 46 showed continued response in all lesions (Figure 3B). The patient remains on pembrolizumab monotherapy and overall continues to do well 32 months after initiating immunotherapy.

Discussion

Rare cancers such as UCOGC present unique clinical challenges for oncology treatment teams. Treatments are often derived from more commonly diagnosed diseases, with the hope that they will be effective and provide

Figure 3. (A) Coronal CT reconstruction showing primary tumor bulk at initiation of pembrolizumab, measuring 33 cm (left panel), and after 24 months of therapy, measuring 11.1 cm (right panel). This image signifies substantial reduction in UCOGC tumor size and enhancement. Bars indicate coronal extent of tumor. (B) Chest CT showing right upper lobe pulmonary metastasis at initiation of pembrolizumab (left panel) and after 24 months of therapy (right panel), signifying complete resolution of the pulmonary metastasis. Arrows indicate the site of disease. Abbreviation: UCOGC, undifferentiated carcinoma with osteoclast-like giant cells.

benefit.¹⁴ Given the low disease incidence and paucity of available clinical outcomes data, evidence-based guidelines for the treatment of UCOGC do not exist, even as part of broader PDAC treatment guidelines. In the United States, neither the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for PDAC nor the ASCO guidelines for

curable or metastatic PDAC offer guidance on UCOGC treatment.^{15–17} Similarly, the ESMO recommendations mention UCOGC's variance but do not discuss possible treatments in either the localized or the metastatic setting.¹⁸ When faced with rare and aggressive malignancies, treating physicians must use all available clinical data to guide

therapy. Use of NGS and surrogate biomarkers may provide an opportunity to better target these difficult-to-treat tumors.

Modern genetic sequencing techniques such as NGS have become widespread to better meet the needs of patients with cancer, particularly those with rare or advanced diseases. More than two-thirds of medical oncologists in the United States report having used NGS to inform clinical care decisions.¹⁹ NGS has identified a subset of patients for whom specialized treatments may be available. For example, this modality may identify microsatellite-unstable noncolorectal cancers that may benefit from immunotherapy.^{20,21} TMB has been used as a predictive biomarker for response to inhibitors of PD-1 or its ligand, PD-L1. Prior research has shown improved treatment responses to immunotherapies in various cancers, such as melanoma, ovarian cancer, and non-small cell lung cancer. For example, Goodman et al²² found that in a group of diverse cancers, higher TMB (≥ 20 mut/Mb) was associated with improved outcomes with PD-1/PD-L1 checkpoint inhibitors. Given these and other data, on June 16, 2020, the FDA approved pembrolizumab for use in unselected cancers with a TMB of ≥ 10 mut/Mb measured by the FoundationOneCDx companion diagnostic test (Foundation Medicine, Cambridge, MA).

Unfortunately, patients with PDAC generally have not benefited from PD-1/PD-L1 blockade.^{11,23} However, Lehrke et al²⁴ recently showed that undifferentiated pancreatic carcinomas (including UCOGC) displayed enrichment of PD-L1 on tumor cells, particularly when compared with conventional PDAC tumors. Undifferentiated carcinomas were >4 times as likely to have $\geq 1\%$ PD-L1 expression compared with unselected PDAC (63% vs 15%, respectively; $P < .01$). Tumors with $\geq 10\%$ PD-L1 expression were >2 times as likely to be undifferentiated carcinomas compared with unselected PDAC (87% vs 43%, respectively; $P < .05$).

Building upon this work, Luchini et al²⁵ created a larger series of UCOGC, finding a similar PD-L1 expression rate on tumor cells (63%). The investigators reported that UCOGC with a mixed component of PDAC were significantly more likely to express PD-L1 than tumors that were purely UCOGC (81.2% vs 36.3%, respectively; $P = .040$). In contrast to the work by Lehrke et al,²⁴ Luchini et al²⁵ found that in adjusted multivariate models, PD-L1 positivity was significantly associated with reduced OS compared with PD-L1 negativity; TMB was not assessed.

In another report, Humphris et al²⁶ assessed TMB in 385 pancreatic cancers and found that only 5 patients had a hypermutated phenotype with a TMB >20 ; 4 had loss of mismatch repair proteins and 1 did not. However, the TMB assessment of that single patient was assessed on a tumor-derived cell line, ATCC CRL-2551. It is not clear whether the elevated TMB was present in the original tumor or was a consequence of immortalization. It is also not clear whether this cell line was made from a UCOGC or some other undifferentiated subtype of pancreatic cancer.

Finally, we read with interest a recent publication by Obayashi et al²⁷ about a similar patient in whom pulmonary metastases from UCOGC pancreatic cancer responded to checkpoint inhibitors. However, TMB was not assessed in this patient, and the patient received treatment meant for a presumed lung cancer. The true diagnosis only became clear with time, and the residual pancreatic primary was successfully resected. Our case report adds to the expanding body of literature showing the use of TMB as a predictive biomarker for treatment with a checkpoint inhibitor in this rare disease. A larger prospective study assessing NGS and PD-1/PD-L1 staining as predictive biomarkers in undifferentiated carcinomas (including UCOGC) could provide much-needed data to paint a truer picture of this rare disease entity.

Conclusions

This is the first report demonstrating continued response of pancreatic UCOGC to a PD-1/PD-L1 blockade even without resection. Furthermore, ours is the first reported patient with UCOGC that metastasized to the brain. NGS was an important step in identifying the patient's high TMB and selecting a PD-L1 inhibitor for the third line of therapy. Given the aggressive nature of undifferentiated pancreatic cancers, using NGS and PD-1/PD-L1 testing to further optimize earlier lines of treatment from which patients can derive the most benefit may be an important step in improving outcomes.

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