CASE REPORT

Differentiation Syndrome in a Patient With NSCLC Harboring *IDH2* Mutation Treated With Enasidenib: Case Report

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ABSTRACT

IDH2 gain-of-function mutations cause DNA hypermethylation interfering with cellular differentiation and are linked to poor disease outcomes in NSCLC. *IDH2*-inhibitor enasidenib is approved for refractory acute myeloid leukemia but has been associated with delayed onset of differentiation syndrome—a potentially fatal inflammatory reaction caused by differentiating agents, namely all-trans retinoic acid and arsenic trioxide. We report the first case of differentiation syndrome in a patient with NSCLC treated with enasidenib, who after 7 weeks experienced bilateral peripheral edema and shortness of breath, with scans exhibiting pericardial effusion and ground-glass opacities suggestive of pneumonitis. Differentiation syndrome should be considered as a differential diagnosis in patients with solid tumors undergoing *IDH2*-inhibitor targeted therapy.

Keywords: Enasidenib; IDH2 inhibitor; Differentiation syndrome; Non–small cell lung cancer; Case Report

Introduction

Differentiation syndrome (DS) was first characterized as a symptom complex including fever, respiratory distress, edema, and pleural or pericardial effusions.[1] It is known to be a potentially fatal complication associated with acute myeloid and promyelocytic leukemia patients undergoing induction treatment with all-trans retinoic acid (ATRA) and arsenic trioxide (ATO). Previous case reports suggest that radiographic findings of ground-glass opacity, lower lung lobe lesions, and pericardial or pleural effusion are supportive of clinical diagnosis of DS.[2]

With a better understanding of cancer genomics, newer therapies that target particular oncogenetic mutations have become the standard of care. *IDH2*-inhibitor enasidenib was approved in 2017 for the treatment of refractory acute myeloid leukemia (AML) with detectable *IDH2* mutation, and recent clinical trial results have reported potential antitumor activity of *IDH1* and *IDH2* inhibitors in the treatment of solid tumors including NSCLC.[3] Here, we present the first case of DS in a patient with NSCLC treated with enasidenib for targeting IDH2 mutation.

Case Presentation

A 54-year-old female patient with no relevant past medical history presented for evaluation of exertional

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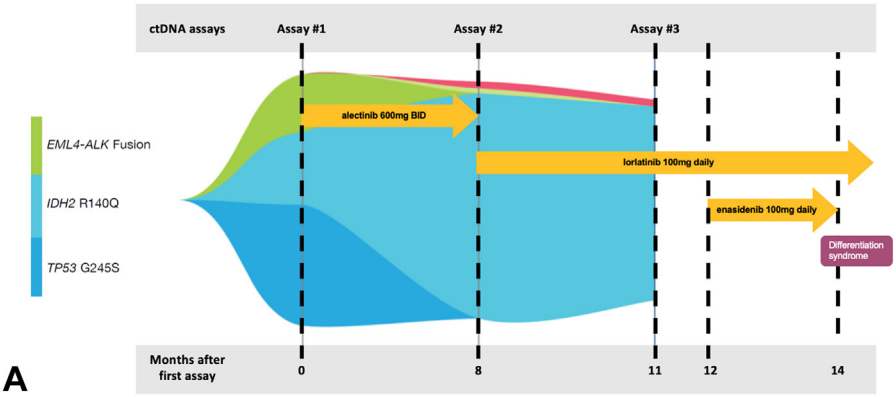

% cfDNA Detected of Relevant Biomarkers

	Guardant 360 assay		
Detected biomarkers	**#1: 0 months**	**#2: 8 months**	**#3: 11 months**
***IDH2* R140Q**	13.7%	23.8%	18.8%
***EML4-ALK* Fusion**	10.1%	ND	ND
***TP53* G245S**	25.9%	ND	ND

B

ND = Not Detected

Figure 1. (*A*) Tumor response map (Guardant360) showing frequencies of detected somatic mutations across the treatment timeline, with *IDH2* mutation in light blue. (*B*) Table of detected allele frequencies corresponding to the tumor response map. #, number; cfDNA, cell-free DNA; ctDNA, circulating tumor DNA.

shortness of breath, fatigue, and unintentional weight loss of about 15 lbs in 2 to 3 months. A review of systems was notable for mild anxiety, intermittent dizziness, and visual disturbances. The patient was a former smoker who had quit within 1 year before the presentation, with a family history of lung cancer in both parents who were smokers as well. The patient was diagnosed with programmed death-ligand 1–negative lung adenocarcinoma with a 1.3-cm nodule in the right upper lobe of the lung, along with multiple bilateral lung lesions and lymphadenopathy. A hypoechoic 1.2 cm lesion was detected in the right hepatic lobe concerning the metastatic disease. Computed tomography (CT) brain was obtained, which did not reveal any acute abnormalities nor evidence of metastatic disease; magnetic resonance imaging of the brain performed 2 weeks after was also negative, with no evidence of metastasis. Furthermore, the bone scan was negative for skeletal metastasis. Blood-based circulating tumor DNA (ctDNA) assay using Guardant360 (Guardant Health, Redwood City, California) revealed *EML4-ALK* fusion at a variant allele frequency of 10.1% and *IDH2* mutation at 13.7% (Fig. 1*A* and *B*). Tissue next-generation sequencing using Tempus similarly revealed *EML4-ALK* chromosomal rearrangement, and TP53 and RB1 loss of function somatic mutations.

The patient was started on *ALK*-inhibitor alectinib with good clinical response, including decreased primary nodule size and resolution of the liver lesion and multiple bilateral lung lesions. After 8 months, disease progression was noted with the emergence of two new liver lesions. Repeat ctDNA assay revealed *IDH2*-mutant allele frequency had increased to 23.8%. The patient was switched to lorlatinib, but mild disease progression was observed after 3 months with new ground-glass opacities, lung lesions, and moderate pericardial effusion. *IDH2* mutation was still detected at 18.8%, whereas other mutations including *ALK* fusion remained nondetectable on repeat ctDNA assay. Enasidenib was added as a targeted therapy at 100 mg daily—as it is not approved by the U.S. Food and Drug Administration in lung cancer, enasidenib was delivered off-label in an experimental setting.

The patient exhibited good tolerability without adverse symptoms for the first 2 weeks. After 7 weeks on enasidenib, the patient reported a recurrence of bilateral lower extremity edema and new-onset shortness of breath. Chest CT revealed large pericardial effusion (Fig. 2*A* and *B*) and increased bilateral ground-glass opacities (Fig. 2*C*–*F*), whereas previously measured pulmonary nodules remained stable and unchanged in size. No evidence of new metastatic disease outside the thoracic cavity was noted from the CT abdomen-pelvis. These results favored pneumonitis and inflammation as opposed to disease progression. Echocardiogram revealed a left ventricle ejection fraction of 64%, compared with a baseline of 74% approximately 1 year before, with large circumferential pericardial effusion and the presence of two out of five echocardiographic

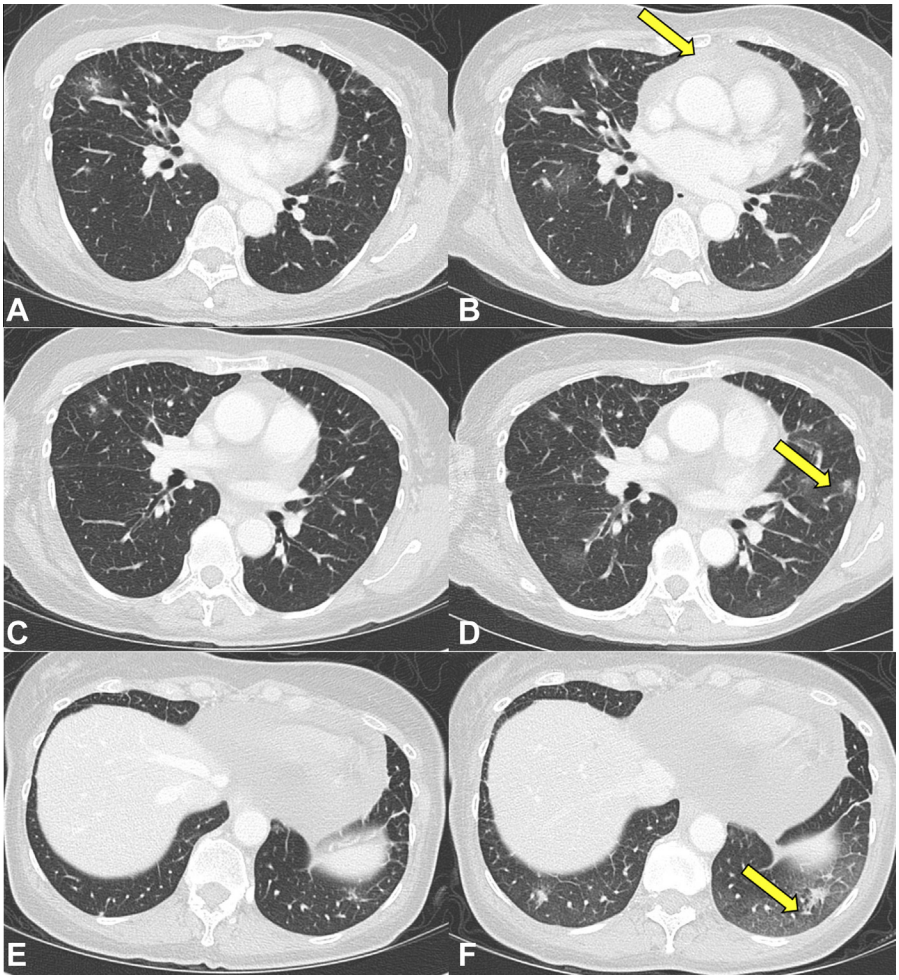

Figure 2. Chest CT with focus on the lungs, before enasidenib was started (*A*, *C*, *E*) and immediately before discontinuation (*B*, *D*, *F*). Increased pericardial effusion (*B*) and progressive ground-glass opacity in the lingula (*D*) and left lower lobe (*F*) are evident, consistent with DS. CT, computed tomography; DS, differentiation syndrome.

signs for tamponade; however, the patient remained hemodynamically stable.

Enasidenib was discontinued immediately for strong suspicion of DS. The patient was treated with tapering doses of oral dexamethasone with a dosing of 10 mg followed by 5 mg, 2 mg, and 1 mg twice daily tapered down after 3 days of each dose. Follow-up CT 1 month after the discontinuation of enasidenib revealed resolution of edema and reduced effusion and pneumonitis. The patient was monitored for symptoms of DS for several months. Sufficient recovery was determined after 4 months, and the patient was switched to a chemoimmunotherapy regimen.

Discussion

To the best of our knowledge, this is the first case of DS in a patient with NSCLC treated with enasidenib targeting *IDH2* mutation. *IDH2* mutations in NSCLC are associated with smoking history and poor clinical presentation but are relatively uncommon. We hypothesized that enasidenib may carry a beneficial role for our patient who was noted to have persistently elevated *IDH2* levels and progression of disease during treatment with lorlatinib. Immediately after enasidenib introduction, our patient reported good tolerance and possible clinical improvement. However, this was limited by the development of the DS with emerging shortness of breath, worsening peripheral edema, and massive pericardial effusion 53 days after the start of enasidenib. No ctDNA assay was obtained after the start of enasidenib because the drug was prematurely discontinued, so the response of *IDH2* mutation level could not be assessed.

In the supporting trial for Food and Drug Administration approval of enasidenib in refractory AML, patients who were given enasidenib exhibited good tolerance, induction of hematologic response, and a median survival of greater than 9 months compared with 3 months in patients treated with standard ATRA and ATO therapy.[4] Recent clinical trials have also reported preliminary results suggesting the potential antitumor activity of *IDH1*

and *IDH2* inhibitors in solid tumors.[3] Although the occurrence of DS in AML is lower in patients treated with enasidenib (10%) versus ATRA and ATO (19%–20%), the median time to onset is much longer at 48 days compared with 11 days.[5]

One study found IDH2 mutations to be branching mutations more prominent in certain subclonal populations of tumor cells harboring a driver mutation.[5] The authors analyzed next-generation sequencing results from 1924 lung cancer specimens to detect mutations in IDH1 and IDH2 genes and several others. IDH2 mutations were found to occur in NSCLC tumor cells harboring concurrent driver mutations, namely KRAS followed by EGFR and PIK3CA. One sample revealed two distinct IDH2 mutations, which evolved in parallel among subpopulations with the same trunk KRAS driver mutation, suggesting the driver mutation is primarily responsible for the initiation process and IDH2 mutation may then occur in the subclonal population of tumor cells. The authors hypothesized a combinatory therapy including trunk driver targeting could offer better outcomes.

To estimate pathogenicity, we analyzed the *IDH2* mutation using six widely used in silico tools (Polyphen-2, Align-GVGD, MutationTaster2021, CADD, CONDEL, and REVEL). It was found to be pathogenic in three tools, benign in one tool, and two were not able to categorize it. On the basis of this estimation and ctDNA results, we speculate that the mutation is pathogenic, and thus, could be targeted by an *IDH2* inhibitor. However, in NSCLC, the targetability of *IDH2* mutation remains to be elucidated.

Conclusions

This is the first case of DS in a patient with NSCLC treated with enasidenib targeting *IDH2* mutation. In AML, the occurrence of DS is well established in patients treated with the previous standard of care ATRA and ATO and *IDH2*-inhibitor enasidenib. Caution for early identification of DS is necessary for patients with solid tumors undergoing *IDH2*-inhibitor targeted therapy.

CRediT Authorship Contribution Statement

Bhoomika Sukhadia: Conceptualization, Investigation, Writing - original draft.

Dean Tan: Writing - original draft, Writing - reviewing and editing.

Youjin Oh: Data Curation, Writing - reviewing and editing.

Zunairah Shah: Resource, Writing - reviewing and editing.

Young Kwang Chae: Supervision, Writing - reviewing and editing.

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The patient consented to the experimental treatment and provided written informed consent for the publication of details in this case report. No sources were used for funding.

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