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Case Report

Fatal Eosinophilic Myocarditis after Monoclonal Antibody TherapyAdministration

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Abstract

Background: Cetuximab and programmed cell death protein 1 (PD-1) inhibitors are now commonly used in the treatment of a number of advanced cancers. Here we report a case of fatal eosinophilic myocarditis in a patient receiving the combination of cetuximab and PD-1 inhibitor, pembrolizumab.

Methods: After informed consent from next of kin, an autopsy was conducted. Virology testing was performed.

Results: Based on the temporal exposure of cetuximab, lack of detectable viral infection, and previous reported cases of cardiac arrest with cetuximab dosing and cardiac signaling abnormalities, we believe that the cause of eosinophilic myocarditis is most likely cetuximab.

Conclusion: Myocarditis due to monoclonal antibody therapy is exceedingly rare, it is important for clinicians to be vigilant about this potential complication, especially if these agents will have expanded use and application in the neoadjuvant or adjuvant setting with curative intent.

Key words: Eosinophilic myocarditis; Autopsy; Cetuximab; PD-1 inhibitor

Introduction

Cetuximab, a monoclonal antibody directed at the Epidermal Growth Factor Receptor (EGFR), is used as a systemic chemotherapeutic agent in EGFR-expressing advanced-stage carcinomas, including cancers of the head and neck, colorectal cancer, and lung. Common side effects for cetuximab include skin rash, diarrhea, and/or infusion reaction and are often manageable with symptomatic support.

In the last few years, there has been a number of new immunotherapy monoclonal antibodies approved. Use of checkpoint monoclonal antibody inhibitors that block programmed cell death protein 1 (PD-1) such as nivolumab and pembrolizumab, will undoubtedly riseas their on-label indications across multiple tumor types increase [1]. Currently, PD-1 inhibitors are approved for use in a multitude of cancers including Hodgkin's lymphoma, melanoma, renal cell, urothelial cell, non-small cell lung, and head and neck cancers. PD-1 inhibitor side effects include immune-related adverse events and when severe are managed with administration of high-dose glucocorticoids2. The utilization of PD-1 inhibitors in combination with other monoclonal antibodies, targeted therapies, and/or cytotoxic chemotherapy is currently under exploration in hundreds of clinical trials [1].

In rare instances, fatal events have been reported with cetuximab and PD-1 inhibitors. For cetuximab, a 2-3%rate of cardiopulmonary arrest and/or sudden death is reported [2].

Myocarditis with immunotherapy is reported to be exceedingly rare [3], with a rate of 0.06 to 0.27% [2], the higher rates with combination immunotherapy, with a median onset of ~10 weeks1. More recently, fatal myocarditis due to PD-1 inhibitor therapy has also been described with an incidence rate of 0.03% [4].

Here we report a case of fatal eosinophilic myocarditis in a patient receiving the combination of cetuximab and pembrolizumab.

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Materials and Methods

Ethics Statement

This patient was treated as part of a clinical trial in accordance with the Declaration of Helsinki and was approved by the Western Institutional Review Board (NCT02318901).

After informed consent from next of kin, an autopsy was conducted. Virology testing using DNA from this individual was used for virus-specific PCR amplification and RNA from this individual was used for virus-specific reverse transcriptase PCR. The resulting PCR products were analyzed by agarose gel electrophoresis in a CLIA and CAP certified laboratory.

Results

A 60-year-old woman originally diagnosed approximately 3.5 years earlier with stage IIIA pT2pN1aM0 adenocarcinoma of the colonunderwent a partial colectomy of the transverse colon. Tumor testing revealed her cancer was wildtype for KRAS, NRAS, BRAF, and PIK3CA genes. She completed 6 months of adjuvant FOLFOX chemotherapy and about 2.5 years later was found to have biopsy proven liver metastasis. Her past medical history was significant for diverticulosis, hypertension, hand eczema, and smoking-related asthma from a 30 pack-year history of smoking. She was consented and enrolled on a phase Ib clinical trial of capecitabine, irinotecan, and nivolumab (NCT02423954). After 3 months on study, she was taken off study for disease progression. She then consented and enrolled on a phase Ib trial of cetuximab and pembrolizumab (NCT02318901). She was tolerating treatment well and received 2 doses of the combination and 2 doses of cetuximab single agent without incident. Dosing of cetuximab was 400 mg/m2 on cycle 1 day 1 and 250 mg/m2 on cycle

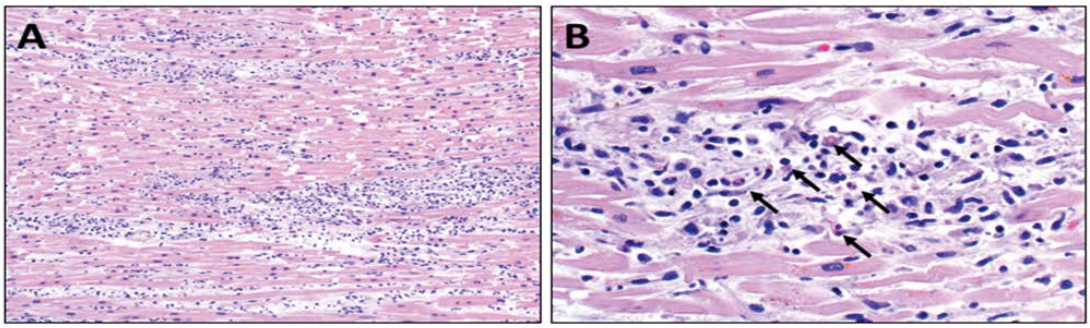

Figure 1. Representative photomicrographs of myocardium at autopsy.

(A) At low power, patchy chronic inflammatory infiltrates are present throughout the myocardium, associated with myocyte loss and myocardial edema.

(B) At higher power, the infiltrate is composed of lymphocytes, histiocytes, and numerous eosinophils (arrows), and is associated with myocyte destruction and loss; however, giant cells are absent. Hematoxylin & eosin, original magnifications 100x (A) and 400x (B).

1 day 8; thereafter, day 1 and 8 of each 21-day cycle were 250 mg/m2. Dosing of pembrolizumab was 2 mg/kg on day 1 of every 21-day cycle.

At her last visit in clinic (day 29 on study), the patient denied chest pain and her baseline shortness of breath attributed to her asthma had improved after using budesonide/formoterol inhaler without the need for rescue inhalers. Herhand eczema improved with use of clobetasol cream and her symptoms of gastroesophageal reflux improved with ranitidine. She had stable mild peripheral sensory neuropathy of the fingers and feet. Other symptoms were negative including: nausea, vomiting, diarrhea, constipation, headaches, cough,and vision or hearing changes. Her appetite was good; she had mild fatigue, and denied any pain. Overall, she had a Karnofsky Performance Status of 90%. Her vital signs were within normal limits and her physical examination was unrevealing. Blood count, serum chemistries, and hepatic function tests were all within normal limits. Her CEA was trending down from 16.6 ng/mL just prior to initiation of treatment on study to 6.3 ng/mL on day 22 of study, suggesting that her tumor may be responding to therapy.

On day 30 on study, the patient was at home and reportedly not feeling well and had a syncopal episode. Emergency services were called, vital signs were taken, and she was considered stable. Patient had another syncopal episode, emergency services responded again, though this time the patient was in cardiac arrest. Chest compressions were performed, and patient could not be resuscitated. Patient was pronounced dead. Family gave permission for an autopsy.

An autopsy was performed and the cause of death was determined to be eosinophilic (hypersensitivity) myocarditis, with representative sections of myocardium illustrated in Figure 1. The cardiac specimen was sent for viral testing and adenovirus, cytomegalovirus, Epstein-Barr virus, enterovirus, and parvovirus were not detected.

Discussion

This patient had received prior PD-1 in combination with cytotoxic chemotherapy without incident over the course of 3 months (at total of 6 doses of nivolumab at 3 mg/kg every 14 days). At least 21 days elapsed between her last dose on that study and initiation of treatment with pembrolizumab and cetuximab. The autopsy findings did not point to any of her pre-existing comorbidities as contributing causes to her death. Based on the temporal exposure of cetuximab and prior exposure to PD-1 over the course of at least 3 months without incident, lack of detectable viral infection, and previous reported cases of cardiac arrest with cetuximab dosing [5] and cardiac signaling abnormalities [6], we believe that the cause of eosinophilic myocarditis is most likely cetuximab, and unlikely due to pembrolizumab. While myocarditis due to monoclonal antibody therapy is exceedingly rare, it is important for clinicians to be vigilant about this potential complication, especially if these agents will have expanded use and application in the neoadjuvant or adjuvant setting with curative intent.

Conclusions

Cetuximab was the likely cause of fatal eosinophilic myocarditis. Further investigation to help identify those at risk for monoclonal antibody induced myocarditis is warranted to better direct therapeutic selection.

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Disclosures

GJW has the following disclosures: Circulogene-consulting, ownership interest, Paradigm-consulting, Angiex-consulting, Igynta-honoraria, Pfizer-honoraria, IDEA Pharma-honoraria, GLG Council-consulting, Guidepoint Global-consulting, Cambridge Healthtech Institute- travel and accommodation expenses, Tesaro- travel and accommodation expenses, issued patent PCT/US2011/020612, outside the submitted work, Western Regional Medical Center-employment at the time of investigation.

CC has the following disclosure: Western Regional Medical Center-employment at the time of investigation.

The other authors have no disclosures to declare.

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