CASE IN POINT

# What We Have Learned About Combining a Ketogenic Diet and Chemoimmunotherapy: a Case Report and Review of Literature

**Daniel Sims, MD[a]; Agnes K. Liman, MD[b]; Victoria Leung, PharmD[b]; Andrew Hwang, MD[a]; Jeffrey Means, MD[a]; Andrew D. Liman, MD[a,b]**

**Background:** A high-fat, moderate-protein, low-carbohydrate ketogenic diet has been reported in the literature as a treatment option for patients with cancer.
**Case Presentation:** A 69-year-old veteran was initially diagnosed with stage III colorectal cancer and progressed to having liver, pancreatic, and omental lymph node involvement despite completing adjuvant FOLFOX (fluorouracil, leucovorin calcium, and oxaliplatin) after surgery. The patient was treated with FOLFIRI (fluorouracil, leucovorin calcium, and irinotecan hydrochloride) and bevacizumab, followed by encorafenib and cetuximab on progression. Subsequently, he received pembrolizumab but continued to progress. The patient was later placed on trifluridine/tipiracil and bevacizumab concurrent with a ketogenic diet. Positron emission tomography and carcinoembryonic antigen levels indicated disease stabilization for 10 months. On progression, the patient was transitioned to ipilumimab and nivolumab and continued to adhere to the ketogenic diet. The patient's disease has continued to remain stable for the past 1 year. His degree of ketosis was determined using the glucose ketone index. The patient continues to have a good quality of life during concurrent ketogenic diet and therapy.
**Conclusions:** This case supports the tolerability of the ketogenic diet along with chemotherapy and immunotherapy and should be considered as an adjunct to standard cancer treatment. In this report, we reviewed the latest literature about cellular mechanism of the ketogenic diet and the efficacy and relationship with chemotherapy and immunotherapy. We are about to open a ketogenic diet protocol at the Veterans Affairs Central California Health Care System in Fresno.

Author affiliations can be found at the end of this article.
**Correspondence:** Andrew Liman (andrew.liman@va.gov)

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Originally developed for the treatment of refractory epilepsy, the ketogenic diet is distinguished by its high-fat, moderate-protein, and low-carbohydrate food program. Preclinical models provide emerging evidence that a ketogenic diet can have therapeutic potential for a broad range of cancers. The Warburg effect is a condition where cancer cells increase the uptake and fermentation of glucose to produce lactate for their metabolism, which is called aerobic glycolysis. Lactate is the key driver of cancer angiogenesis and proliferation.[1,2]

The ketogenic diet promotes a metabolic shift from glycolysis to mitochondrial metabolism in normal cells while cancer cells have dysfunction in their mitochondria due to damage in cellular respiration. The ketogenic diet creates a metabolic state whereby blood glucose levels are reduced, and blood ketone bodies (D-β-hydroxybutyrate and acetoacetate) are elevated. In normal cells, the ketogenic diet causes a decrease in glucose intake for glycolysis, which makes them unable to produce enough substrate to enter the tricarboxylic acid (TCA) cycle for adenosine triphosphate (ATP) production. Fatty acid oxidation plays a key role in ketone body synthesis as a "super fuel" that enter the TCA cycle as an alternative pathway to generate ATP. On the other hand, cancer cells are unable to use ketone bodies to produce ATP for energy and metabolism due to mitochondrial defects. Lack of energy subsequently leads to the inhibition of proliferation and survival of cancer cells.[3,4] The ketogenic diet also works via the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt) signaling pathway, which is one of the most important intracellular pathways for tumor cells (Figure 1).

We previously published a safety and feasibility study of the Modified Atkins Diet in metastatic cancer patients after failure of chemotherapy at the US Department of Veterans Affairs (VA) Pittsburgh Healthcare System.[1] None of the patients were on chemotherapy at the time of enrollment. The Modified Atkins Diet consists of 60% fat, 30% protein, and 10% carbohydrates and is more tolerable than the ketogenic diet due to higher amounts of protein. Six of 11 patients (54%) had stable disease and partial response on positron emission tomography/computed tomography (PET/CT). Our study showed that patients who lost at least 10% of their body weight had improvement in quality of life (QOL) and cancer response.[1] Here we present a case of a veteran with extensive metastatic colon cancer on concurrent ketogenic diet and chemotherapy subsequently followed

by concurrent ketogenic diet and immunotherapy at Veterans Affairs Central California Health Care Systems (VACCHCS) in Fresno.

## CASE PRESENTATION

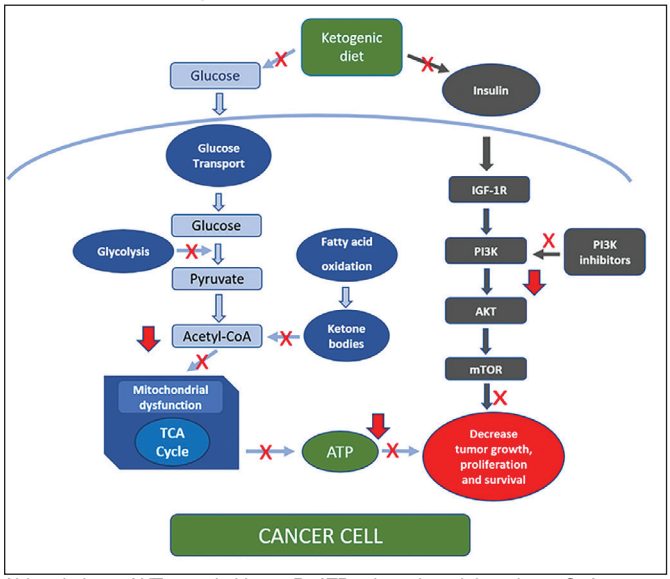
A 69-year-old veteran had iron deficiency anemia (hemoglobin, 6.5 g/dL) about 5 years previously. He underwent a colonoscopy that revealed a near circumferential ulcerated mass measuring 7 cm in the transverse colon. Biopsy results showed mucinous adenocarcinoma of the colon with a foci of signet ring cells (Figure 2). He underwent a laparoscopic-assisted extended right hemicolectomy and partial omentectomy 2 months later. His surgical pathology revealed mucinous adenocarcinoma with 22 out of 45 lymph nodes, consistent with stage IIIC colon cancer (pT3pN2bM0).

The patient received adjuvant treatment with FOLFOX (fluorouracil, leucovorin calcium, and oxaliplatin), but within several months he developed pancreatic and worsening omental metastasis seen on PET/CT. He was then started on FOLFIRI (fluorouracil, leucovorin calcium, and irinotecan hydrochloride) plus bevacizumab 16 months after his initial diagnosis. He underwent a pancreatic mastectomy that confirmed adenocarcinoma 9 months later. Afterward, he briefly resumed FOLFIRI and bevacizumab. Next-generation sequencing testing with Foundation One CDx revealed a wild-type (WT) *KRAS* with a high degree of tumor mutation burden of 37 muts/Mb, *BRAF* V600E mutation, and high microsatellite instability (MSI-H). Immunohistochemistry staining showed the loss of nuclear expression of *MLH1* and *PMS2* (Figure 3).

Due to disease progression, the patient's treatment was changed to encorafenib and cetuximab for 4 months before progressing again with new liver mass and mediastinal lymphadenopathy. He then received pembrolizumab for 4 months until PET/CT showed progression and his carcinoembryonic antigen (CEA) increased from 95 to 1031 ng/mL by January 2021 (Figure 4).

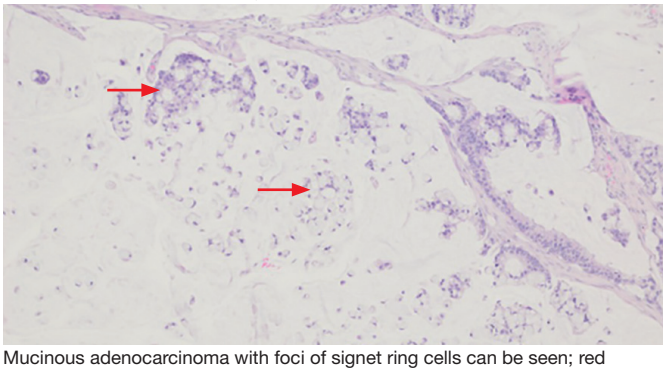
The patient was started on trifluridine/tipiracil, and bevacizumab while concurrently initiating the ketogenic diet in January 2021. Laboratory tests drawn after 1 week of strict dietary ketogenic diet adherence showed low-level ketosis with a glucose ketone index (GKI) of 8.2 (Table 1). Repeat PET/CT 6 months later

**FIGURE 1** Ketogenic Diet and Cellular Mechanism




Abbreviations: AKT, protein kinase B; ATP, adenosine triphosphate; CoA, coenzyme A; IGF, insulin growth factor; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol-3-kinase; TCA, tricarboxylic acid.
Red X, inhibition; red down arrow, downregulation or decrease production. The ketogenic diet decreases glucose entering cancer cells via glucose transport. Cancer cells are unable to use acetyl-CoA substrate due to mitochondrial dysfunction that failed to generate ATP. Cancer cells are unable to use ketone bodies. The ketogenic diet reduces insulin and IGF-1R receptors that caused downregulation of the PI3K/AKT/mTOR pathway and inhibit tumor proliferation and increase apoptosis. PI3K inhibitors prevent the pathway and there is evidence of efficacy by combining the diet and PI3K inhibitors.

**FIGURE 2** Hematoxylin and Eosin Stain



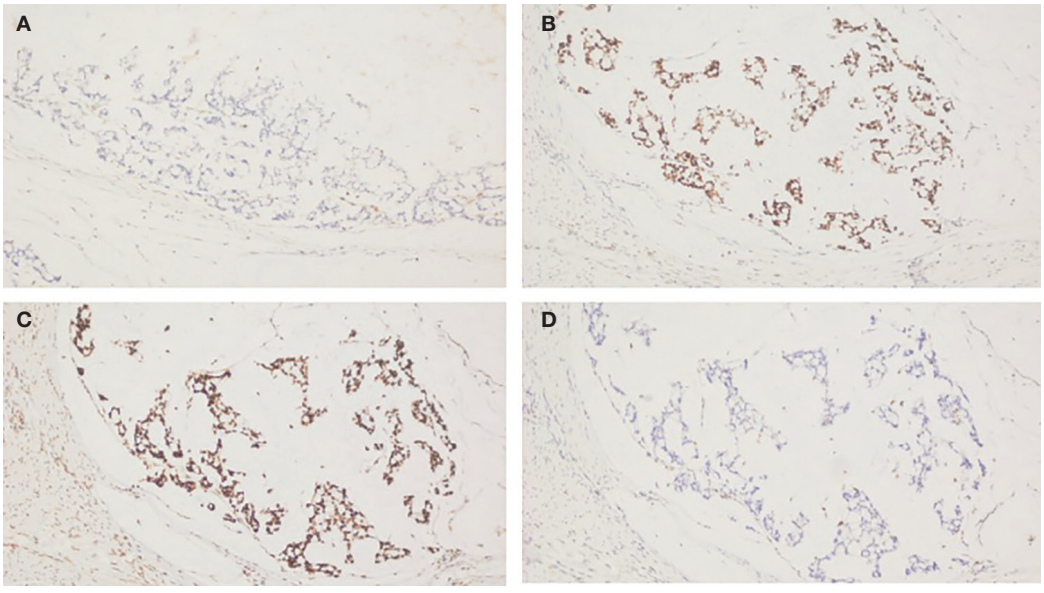
Mucinous adenocarcinoma with foci of signet ring cells can be seen; red arrows depict tumor cells and signet ring cells.

**TABLE 1** Glucose Ketone Index and Ketosis Levels

| Glucose ketone index[a] | Ketosis level |
|---|---|
| ≥ 9 | Not reached ketosis yet |
| 6-9 | Low level of ketosis (ideal for weight loss) |
| 3-6 | Moderate level of ketosis (ideal for type 2 diabetes or insulin resistance) |
| ≤ 3 | High therapeutic level of ketosis (ideal for cancer, epilepsy, and Alzheimer disease) |

[a]Calculated as ([blood glucose in mg/dL]/18)/(blood ketone level in mmol/L).

**FIGURE 3** Immunohistochemistry Stains for Microsatellite Status




A, MLH1; B, MSH2; C, MSH6; D, PMS2. Loss of nuclear expression of MLH1 and PMS2 (zero tumor stained, blue colored) and no loss of nuclear expression of MSH2 and MSH6 (99% tumor stained, brown colored) can be seen.

showed cancer stabilization. His CEA continued to decrease to 23 ng/mL despite less strict dietary adherence, which was reflected in a higher GKI of 56. He intentionally decreased his weight from 184 lb to about 160 lb and remained at this level.

A follow-up PET/CT showed disease progression along with a CEA of 94 ng/mL after 10 months of chemotherapy plus the ketogenic diet (Table 2). Due to MSI-H, we started him on combination immunotherapy with ipilimumab and nivolumab while continuing the ketogenic diet. Adherence to the ketogenic diet has been less strict on immunotherapy; however, serial PET/CT shows cancer stabilization.

The patient continued to experience excellent QOL based on the QOL Eastern Cooperative Oncology Group (ECOG) core quality of life questionnaire (QLC-C30) forms, which he completed every 3 months. Twenty-two months after starting the ketogenic diet, the patient's CEA increased to 293 ng/mL although PET/CT continues to show stable disease (Figures 4, 5, and 6).

## DISCUSSION

The purpose of this case report is to describe whether a patient receiving active cancer treatment was able to tolerate the ketogenic diet in conjunction with chemotherapy or immunotherapy. Most literature published on the subject evaluated the tolerability and response of the ketogenic diet after the failure of standard therapy. Our patient was diagnosed with stage III mucinous colon adenocarcinoma. He received adjuvant chemotherapy but quickly developed metastatic disease to the pancreas and omentum. We started him on encorafenib and cetuximab based on the BEACON study that showed improvement in response rate and survival when compared with standard chemotherapy for patients with *BRAF* V600E mutation.[5] Unfortunately, his cancer quickly progressed within 4 months and again did not respond to pembrolizumab despite MSI-H, which lasted for another 4 months.

We suggested the ketogenic diet and the patient agreed. He started the diet along with trifluridine/tipiracil, and bevacizumab in January 2021. The patient's metastatic cancer stabilized for 9 months until his disease progressed again. He was started on doublet immune checkpoint inhibitors ipilimumab and nivolumab based on his MSI-H and high tumor mutation burden with the continuation of the ketogenic diet until now. The CheckMate 142 study revealed that the combination of ipilimumab and nivolumab in patients with MSI-H previously treated for metastatic colon cancer showed some benefit.[6]

Our patient had the loss of nuclear expression of *MLH1* and *PMS2* (zero tumor stained)

**FIGURE 4** Computed Tomography of Liver Nodule, Pancreatic Mass, and Omental Implants, Month 1

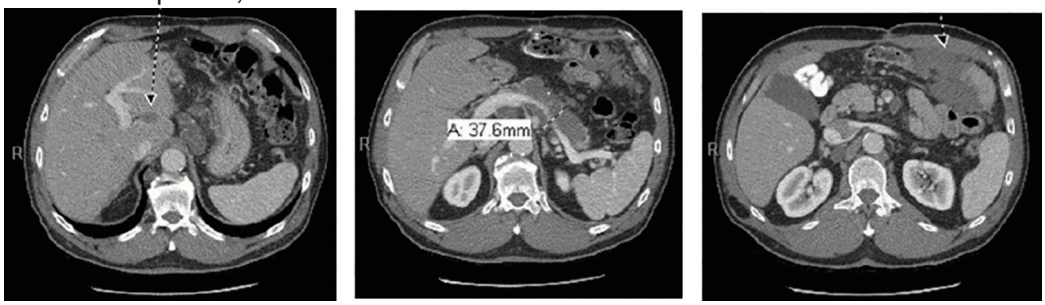



**FIGURE 5** Positron Emission Tomography/Computed Tomography Showing Disease Progression, Month 11

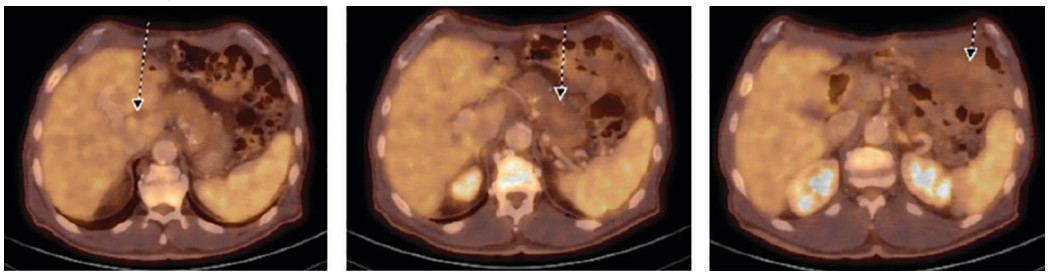
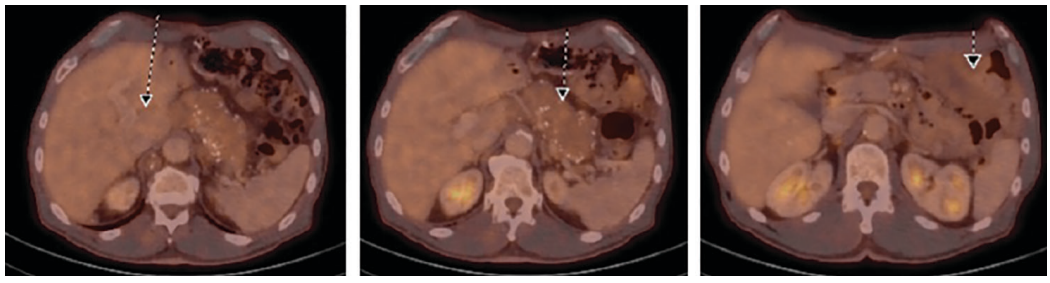


**FIGURE 6** Positron Emission Tomography/Computed Tomography With Pancreatic Calcification and Omental Implants Showing Stable Disease, Month 22



but no evidence of the loss expression of *MSH2* and *MSH6* genes (99% tumor stained). About 8% to 12% of patients with metastatic colon cancer have *BRAF* V600E mutations that are usually mucinous type, poorly differentiated, and located in the right side of the colon, which portends to a poor prognosis. Tumor DNA mismatch repair damage results in genetic hypermutability and leads to MSI that is sensitive to treatment with checkpoint inhibitors, as in our patient. Only about 3% of MSI-H tumors are due to germline mutations such as Lynch syndrome (hereditary nonpolyposis colorectal cancer). The presence of both *MLH1* hypermethylation and *BRAF* mutation, as in our patient, is a strong indication of somatic rather than germline mutation.[7]

GKI, which represents the ratio of glucose to ketone, was developed to evaluate the efficacy of the ketogenic diet. This index measures the degree of metabolic stress on tumor cells through the decrease of glucose levels and increase of ketone bodies. A GKI of ≤ 1.0 has been suggested as the ideal therapeutic goal for cancer management.[8] As levels of blood glucose decline, the blood levels of ketone bodies should rise. These 2 lines should eventually intersect at a certain point beyond which one enters the therapeutic zone or therapeutic ketosis zone. This is when tumor growth is expected to slow or cease.[9] The patient's ketone (β-hydroxybutyrate) level was initially high (0.71 mmol/L) with a GKI of 8.2. (low ketotic level), which meant he tolerated a rather strict diet for the first several months. This was also reflected in his 18 lb weight loss

**TABLE 2** Patient Details During Ketogenic Diet and Chemoimmunotherapy

| Criteria (reference range) | Month 1 | Month 7 | Month 11 | Month 15 | Month 18 | Month 22 |
|---|---|---|---|---|---|---|
| Hemoglobin level, g/dL (14.0-17.0) | 14.2 | 13.5 | 14.1 | 14.9 | 15.3 | 15.1 |
| Carcinoembryonic antigen, ng/mL (< 3.0) | 1031 (high) | 23 (high) | 94 (high) | 20 (high) | 53 (high) | 293 (high) |
| Glucose, mg/dL (70-105) | 105 | 111 | 106 | 103 | 107 | 108 |
| Ketone, β-oxybutyric acid, mmol/L (0.02-0.30) | 0.71 (ideal) | 0.11 (low) | 0.15 (low) | 0.22 (low) | 0.27 (low) | 0.11 (low) |
| Glucose ketone index | 8.2 (low ketosis) | 56 | 39 | 26 | 22 | 54.5 |
| Weight, lb | 184 | 166 | 160 | 167 | 162 | 162 |
| Quality of life | Poor | Better | Better | Better | Better | Better |
| Disease progression on positron emission tomography/computed tomography | Progression | Stable | Progression | Stable | Stable | Stable |
| Chemoimmunotherapy regimen | Trifluridine, tipiracil, bevacizumab | Trifluridine, tipiracil, bevacizumab | Ipilimumab, nivolumab | Nivolumab | Nivolumab | Ipilimumab, nivolumab |

(almost 10% of body weight) and cancer stabilization, as in our previous publication.[1] Unfortunately, the patient was unable to maintain high ketone and lower GKI levels due to fatigue from depleted carbohydrate intake. He added some carbohydrate snacks in between meals, which improved the fatigue. His ketone level has been < 0.5 mmol/L ever since, albeit his disease continues to be stable. The patient continues his daily work and reports a better QOL, based on the ECOG QLC-C30 form that he completed every 3 months.[10] Currently, the patient is still receiving ipilimumab and nivolumab while maintaining the ketogenic diet with stable metastatic disease on PET/CT.

## Ketogenic Diet and Cellular Mechanism of Action

PI3K/Akt (phosphatidylinositol-3-kinase) signaling is one of the most important intracellular pathways for tumor cells. It leads to the inhibition of apoptosis and the promotion of cell proliferation, metabolism, and angiogenesis. Deregulation of the PI3K pathway either via amplification of PI3K by tyrosine kinase growth factor receptors or inactivation of the tumor suppressor phosphatase and tensin homolog (PTEN), which is the negative regulator of the PI3K pathway, contributes to the development of cancer cells.[11]

A study by Goncalves and colleagues revealed an interesting relationship between the PI3K pathway and the benefit of the ketogenic diet to slow tumor growth. PI3K inhibitors inhibit glucose uptake into skeletal muscle and adipose tissue that activate hepatic glycogenolysis. This event results in hyperglycemia due to the pancreas releasing very high levels of insulin into the blood (hyperinsulinemia) that subsequently reactivate PI3K signaling and cause resistance to PI3K inhibitors. The ketogenic diet reportedly minimized the hyperglycemia and hyperinsulinemia induced by the PI3K inhibitor and enhanced the efficacy of PI3K inhibitors in tumor models. Studies combining PI3K inhibitors and ketogenic diet are underway. Hence, combining the ketogenic diet with chemotherapy or other novel treatment should be the focus of ketogenic diet trials.[12,13]

## Ketogenic Diet and Oncology Studies

The impact of the ketogenic diet on the growth of murine pancreatic tumors was evaluated by Yang and colleagues. The ketogenic diet decreased glucose concentration that enters the TCA cycle and increased fatty acid oxidation that produces β-hydroxybutyrate. This event promotes the generation of ATP, although with only modest elevations of NADH with less impact on tumor growth. The combination of ketogenic diet and standard chemotherapy substantially raised tumor NADH and suppressed the growth of murine tumor

**TABLE 3** Ketogenic Modified Atkins Diet Food Composition Protocol

| Food category | Allowed | Prohibited |
|---|---|---|
| Fruits | None | All fresh, dried, or canned |
| Beverage | Water, diet drinks/sodas, liquor, black coffee, tea, tonic water, unsweetened almond milk, soy milk, cashew milk | Wine, beer, regular milk, fruit, regular soda |
| Vegetables | Green leafy, cucumbers, celery, cauliflower, broccoli, mushrooms, kale, spinach, olives, edamame, and green beans | Carrots, potatoes, squash, beans, tomatoes, corn, peas, sauerkraut |
| Meats and protein | Beef, pork, poultry, turkey, lamb, fish, clams, shrimp, bacon, eggs, cream cheese, macadamia, pecan nuts, tofu | Breaded meat or fish, processed cheese products, yogurt |
| Miscellaneous | Splenda, salt, pepper, aspartame, oil, butter, canola oil, mayonnaise, salad dressings | Sugar, honey, juices, syrup, ketchup, fructose, candy, chocolates, ice cream |
| Breads, cereals | None | Pastries, bread products, cakes, pies, popcorn, chips |

cells, they noted.[14] Furukawa and colleagues compared 10 patients with metastatic colon cancer receiving chemotherapy plus the modified medium-chain triglyceride ketogenic diet for 1 year with 14 patients receiving chemotherapy only. The ketogenic diet group exhibited a response rate of 60% with 5 patients achieving a complete response and a disease control rate of 70%, while the chemotherapy-alone group showed a response rate of only 21% with no complete response and a disease control rate of 64%.[15]

The ketogenic diet also reportedly stimulates cytokine and CD4+ and CD8+ T-cell production that stimulates T-cell killing activity. The ketogenic diet may overcome several immune escape mechanisms by downregulating the expression of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) on tumor-infiltrating lymphocytes.[16] Our patient tolerated the combination of the ketogenic diet with ipilimumab (CTLA-4 inhibitor) and nivolumab (PD-1 inhibitor) without significant toxicities and stabilization of his disease.

### Future Directions

We originally presented the abstract and poster of this case report at the Association of VA Hematology/Oncology annual meeting in San Diego, California, in September 2022.[17] Based on our previous experience, we are now using a modified Atkins diet, which is a less strict diet consisting of 60% fat, 30% protein, and 10% carbohydrates combined with chemotherapy and/or immunotherapy. The composition of fat to carbohydrate plus protein in the traditional ketogenic diet is usually 4:1 or 3:1, while in modified Atkins diet the ratio is 1:1 or 2:1. The benefit of the modified Atkins diet is that patients can consume more protein than a strict ketogenic diet and they can be more liberal in carbohydrate allowances. We are about to open a study protocol of combining a modified Atkin diet and chemotherapy and/or immunotherapy as a first-line treatment for veterans with all types of advanced or metastatic solid tumors at VACCHCS. The study protocol was approved by the VA Office of Research and Development and has been submitted to the VACCHCS Institutional Review Board for review. Once approved, we will start patient recruitment. The foods that are allowed vs prohibited in our study are listed in Table 3.

## CONCLUSIONS

Cancer cells have defects in their mitochondria that prevent them from generating energy for metabolism in the absence of glucose. They also depend on the PI3K signaling pathway to survive. The ketogenic diet has the advantage of affecting cancer cell growth by exploiting these mitochondrial defects and blocking hyperglycemia. There is growing evidence that the ketogenic diet is feasible, tolerable, and reportedly inhibits cancer growth. Our case report and previous publications suggest that the ketogenic diet can be added to chemotherapy and/or immunotherapy as an adjunct to standard-of-care cancer treatment while maintaining good QOL. We are planning to open a clinical trial using the modified Atkins diet in conjunction with active cancer treatments as first-line therapy for metastatic solid tumors at the VACCHCS. We are also working closely with researchers from

several veteran hospitals to do a diet collaborative study. We believe the ketogenic diet is an important part of cancer treatment and has a promising future. More research should be dedicated to this very interesting field.

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## Author affiliations
[a]University of California San Francisco Fresno
[b]Veterans Affairs Central California Health Care Systems, Fresno

## Author contributions
*Writing the manuscript*: Daniel Sims. *Writing pathology reports and images*: Agnes Liman. *Writing and reviewing medications*: Victoria Leung. *Writing ketogenic protocol*: Andrew Hwang. *Reviewing the manuscript*: Jeffrey Means. *Writing concept, abstract, history, discussion, and final approval of the manuscript*: Andrew Liman.

## Author disclosures
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## Ethics and consent
The patient in this case report signed a consent for study and for publication. There is no identifiable patient data included in the manuscript.

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