Title
Caution Advised Using Combination Ketoconazole and PD-1 Inhibitors

Journal
AACE Clinical Case Reports, 6(5)

ISSN
2376-0605

Authors
Yang, Yingying
Hecht, Joel R
Liu, Sandy Ting
et al.

Publication Date
2020-09-01

DOI
10.4158/accr-2020-0100

Peer reviewed

Case Report

CAUTION ADVISED USING COMBINATION KETOCONAZOLE AND PD-1 INHIBITORS

Yingying Yang[1]; Joel R. Hecht[2]; Sandy Ting Liu[1]; Melissa J. Cohen[1]; Steven D. Hart[3]; Hanlin L. Wang[3]; Anthony P. Heaney[1]

ABSTRACT

Objective: Immune checkpoint inhibitors are approved to treat multiple cancers. We report life-threatening hepatic failure in 2 consecutive patients with Cushing syndrome that were treated with ketoconazole (KTZ) in combination with 2 different programmed cell death protein 1 (PD-1) inhibitors, Nivolumab and Pembrolizumab.

Methods: The first patient suffered from corticotroph pituitary carcinoma and the second from metastatic adrenal cortical carcinoma. They were both treated with KTZ for tumor-associated hypercortisolism.

Results: Hepatic function was normal on KTZ prior to initiation of PD-1 inhibitors, after which they rapidly developed severe hepatic dysfunction. In both cases, liver biopsy was consistent with drug-induced hepatic injury. Liver function fully recovered on discontinuing KTZ and the PD-1 inhibitors along with methylprednisone therapy.

Conclusion: Antifungal azole therapy is commonly used in oncology patients who may be co-treated with PD-1 inhibitors. Although the specific combination of KTZ and PD-1 inhibitors to treat Cushing syndrome may be relatively uncommon, we recommend careful monitoring of hepatic function using a combination PD-1 inhibitors and azole antifungal agents, especially KTZ, due to the potential of life-threatening hepatic failure. **(AACE Clinical Case Rep. 2020;6:e239-e242)**

Abbreviations:
ACTH = adrenocorticotropic hormone; **CS** = Cushing syndrome; **ICI** = immune checkpoint inhibitor; **KTZ** = ketoconazole; **MRI** = magnetic resonance imaging; **PD-1** = programmed cell death protein 1

INTRODUCTION

Immune checkpoint inhibitors (ICIs) have been approved to treat multiple cancers. Since the introduction of the first programmed cell death protein 1 (PD-1) inhibitor Nivolumab in 2006, more than 2,000 active clinical trials for both PD-1 and its ligand called PD-L1 have been initiated (1). ICIs have also infrequently been used to treat pituitary or adrenal tumors (2,3).

We describe 2 cases of life-threatening hepatic failure where 2 different PD-1 inhibitors, Nivolumab and Pembrolizumab, were each given to 2 patients with Cushing syndrome (CS) receiving ketoconazole (KTZ) to block adrenal cortisol synthesis. Although this combination of KTZ with PD-1 inhibitors to treat CS may be relatively uncommon, the increasing use of PD-1 inhibitors and other ICIs in various cancers and potential combination with other azole antifungals for opportunistic fungal infections in oncology patients warrants highlighting this potentially serious adverse drug interaction.

CASE REPORT

A 68-year-old woman presented with severe headaches. Magnetic resonance imaging (MRI) showed a 2.3-cm pituitary macroadenoma (Fig. 1 *A*). She did not

Submitted for publication February 24, 2020
Accepted for publication April 27, 2020
From the Divisions of [1]Endocrinology and [2]Hematology and Oncology, and the [3]Department of Pathology and Laboratory Medicine, David Geffen School of Medicine at UCLA, University of California, Los Angeles, California.
Address correspondence to Anthony P. Heaney, 200 UCLA Medical Plaza, CA 90095.
E-mail: aheaney@mednet.ucla.edu.
DOI: 10.4158/ACCR-2020-0100

exhibit clinical or biochemical manifestations of hypercortisolism at presentation, but her plasma adrenocorticotropic hormone (ACTH) level was significantly elevated at 179 pg/mL (normal range is <45 pg/mL).

Trans-nasal transsphenoidal surgery confirmed an invasive corticotroph pituitary tumor with a Ki-67 labeling index of 20 to 25%. Despite 2 further trans-nasal transsphenoidal resections and stereotactic radiotherapy, repeated MRI and fluorodeoxyglucose-positron emission tomography with computed tomography demonstrated pituitary tumor progression with cervical lymph node involvement. The tumor was confirmed to be metastatic pituitary carcinoma on fine-needle biopsy (Fig. 1 *B*).

Despite Temozolomide chemotherapy (150 mg/m^2, or 300 mg daily for 5 days) for 9 cycles, her disease progressed further with increased plasma ACTH (466 pg/mL) and she now also exhibited a 4-fold increased 24-hour urinary free cortisol at 200 µg/day (normal range is <50 µg/day). In light of the hypercortisolism, KTZ was started and uptitrated to 800 mg/day over several weeks to attain eucortisolism and she was enrolled in a "basket" clinical trial of Nivolumab taking 3 mg/kg every 2 weeks to control tumor progression. Although her prior liver function had been within normal limits on KTZ, after only 2 doses of Nivolumab the patient was admitted with a 10-fold increase in alanine transaminase and aspartate transaminase levels (Fig. 2 *A*). Abdominal MRI demonstrated a liver of normal size and without evidence of steatosis or focal hepatic lesions.

In a second case, a 48-year-old woman presented with a history of 1-year weight gain, facial swelling, and hirsutism. She was found to have an elevated serum cortisol (20 µg/dL), suppressed ACTH levels (2 pg/mL), and a 6.1-cm right adrenal mass invading the inferior vena cava with 3 hypodense metastatic liver lesions (Fig. 1 *C* and *D*). Right adrenalectomy was performed and pathology confirmed stage IV metastatic adrenal cortical carcinoma. She was initially treated with cisplatin (40 mg/m^2 weekly), mitotane (3 mg/day), and KTZ (1,600 mg/day), the latter to attain eucortisolism.

Ten weeks later, restaging by positron emission tomography with computed tomography demonstrated progressive liver metastases and chemotherapy was changed to EDP-mitotane but both were stopped after 3 months due to severe neuropathy, nausea, and pancytopenia. As part of a clinical trial, intravenous Pembrolizumab (200 mg every 3 weeks) was commenced and KTZ was continued (800 mg/day). Her liver function tests had been within normal limits in prior months, but 1 month after commencing Pembolizumab she reported dark urine, lower back pain, and was found to have a 20-fold increase in alanine transaminase and aspartate transaminase levels in association with ascites (Fig. 2 *B*). Liver ultrasound revealed a smooth contoured liver with heterogeneous parenchyma and multi-

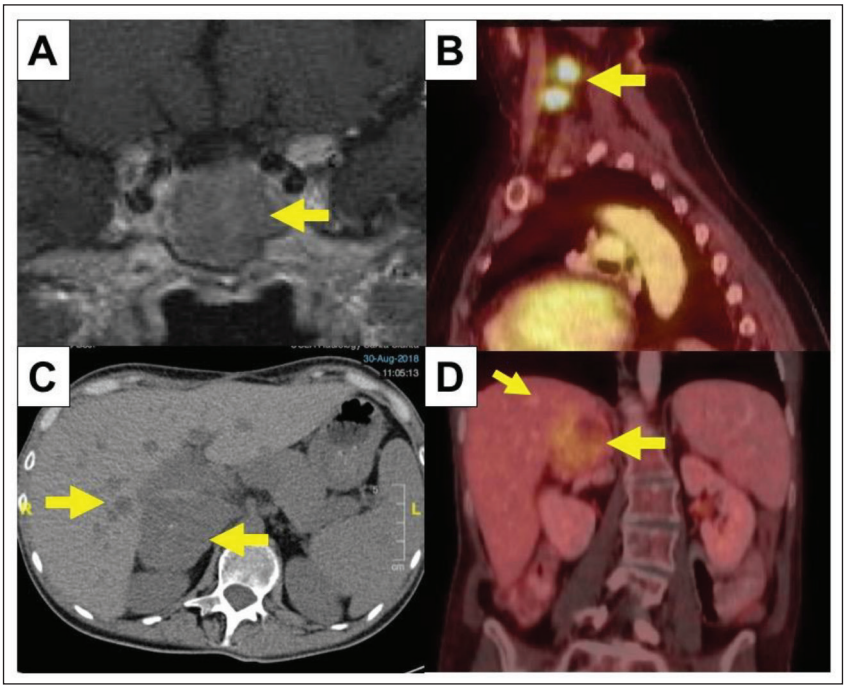

Fig. 1. Coronal contrast-enhanced T1-weighted magnetic resonance image of patient 1's pituitary showing a 2.3-cm sellar mass (*A*). Fluorodeoxyglucose (FDG) positron emission tomography with computed tomography (CT) demonstrating prominent sub-centimeter and peri-centimeter FDG-avid left level 2B and 5 metastatic lymph nodes (*B*). Abdominal CT of patient 2 demonstrating a 2-cm right adrenal mass and hepatic low-density metastases (*C*). FDG positron emission tomography CT demonstrating right adrenal and hepatic metastatic FDG uptake (standard uptake value max 5.5) (*D*). *CT* = computed tomography; *FDG* = fluorodeoxyglucose.

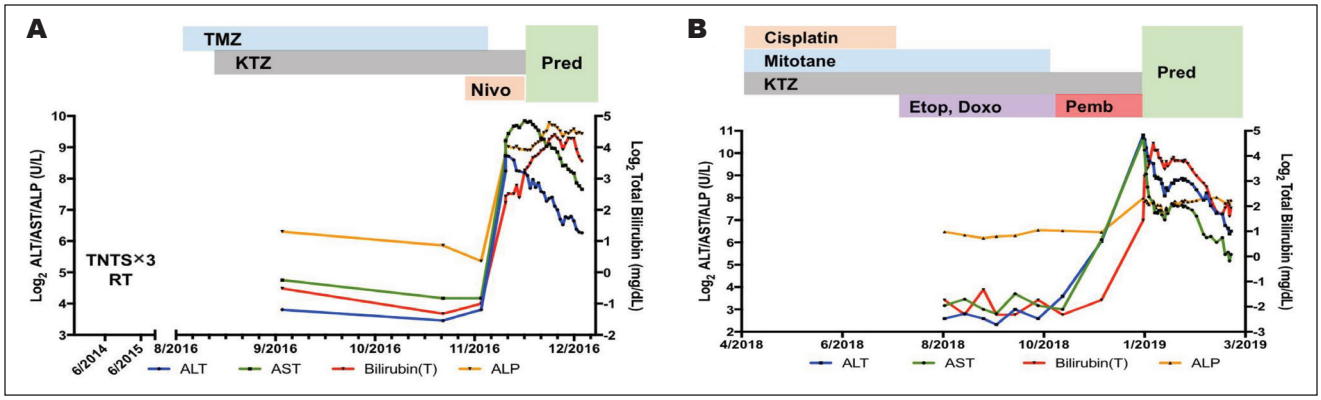

Fig. 2. Liver function tests across various therapies with marked transaminase increase on initiation of PD-1 inhibitor therapy. Patient 1 (*A*) received Nivolumab. Patient 2 (*B*) received Pembrolizumab. *ALP* = alkaline phosphatase; *ALT* = alanine transaminase; *AST* = aspartate transaminase; *Doxo* = Doxorubicin; *Etop* = Etoposide; *KTZ* = ketoconazole; *Nivo* = Nivolumab; *Pemb* = Pembrolizumab; *Pred* = Prednisone; *RT* = radiotherapy; *TMZ* = Temozolomide; *TNTS* = trans-nasal transsphenoidal surgery.

ple hyperechoic masses in keeping with adenoid cystic carcinoma metastases.

In both cases, investigation for other etiologies of acute liver injury including hepatitis panel, tylenol level, antinuclear antibody, anti-smooth muscle antibody, anti-mitochondrial antibody, liver kidney microsome antibody, ceruloplasmin level, ferritin level, and serologies for Epstein-Bar virus, herpes simplex virus, cytomegalovirus, and human immunodeficiency virus were unremarkable. Liver biopsy (Fig. 3) demonstrated acute hepatitis with associated perisinusoidal and periportal fibrosis consistent with drug-induced hepatic injury. Both PD-1 inhibitors and KTZ were discontinued and methylprednisone at 62.5 mg/day was commenced to treat her hepatic injury. Liver function slowly improved and both patients recovered.

DISCUSSION

We have described 2 consecutive patients with hypercortisolism who were treated with a combination of KTZ and PD-1 inhibitors (Nivolumab and Pembrolizumab). Both patients developed severe drug-induced liver injury supported by liver biopsy findings.

KTZ is an approved antifungal agent. Given its action to inhibit cortisol synthesis, it is used "off-label" as a medical therapy for CS (4). Dose-dependent hepatotoxicity occurs in 3 to 4% of patients, and is severe in 1 in 3,000 treated patients (5). Hence, the drug carries a United States Food and Drug Administration black box warning (6). Nonetheless, KTZ was used safely in one study (4) with careful liver function monitoring and only 4 of 200 patients with CS demonstrated a 5-fold to 10-fold elevation in liver enzymes.

Hepatic enzyme increases have also been reported in approximately 6.5% of patients receiving ICIs where histopathological study of the liver shows lymphocyte and histiocyte infiltration with portal fibrosis, some of the features observed in our 2 reported cases (7). Severe liver adverse events appear to be quite rare with PD-1 inhibitor monotherapy, but more frequent with combination treatment by ICIs with other drugs such as decarbazine, sunitinib, and pazopanib (7,8). Of note, there is one prior report of a patient with cortisol-secreting metastatic adrenocortical carcinoma who developed acute liver failure following pembrolizumab added to mitotane therapy (9).

It is possible that KTZ, a known inhibitor of the human hepatic enzymes CYP1A1 and CYP3A4, may have potentiated the hepatotoxicity of the PD-1 inhibitor (10). Due to high efficiency and cost-effectiveness, oral and topical azole derivatives are the most commonly prescribed antifungal drugs with 2.54 million prescriptions in the U.S. (11). Fluconazole and voriconazole accounted for 53% and 11% of prescriptions, respectively. Like KTZ, they have also been reported to induce deranged hepatic function, although liver failure is rare (5). Superficial fungal infections, which affect about 70% of adults, are more common and severe in cancer patients who may be immunosuppressed due to their disease or therapies. In fact, patients receiving ICIs exhibit a 7% increase in serious infection susceptibility, 13% of which are fungal (12). Therefore, the potential for cotreatment with PD-1 inhibitors and azole antifungal agents is extremely high.

We acknowledge that the combination of anti-PD-1 therapy along with KTZ is a very specific drug combination, however we hypothesize that hepatic toxicity could also occur in patients simultaneously treated with anti-PD-1 agents and other azole antifungals. One could argue that given the likelihood of combination treatment with anti-PD-1 agents and various azole derivatives, one might expect these phenomena to have been recognized and reported previously.

CONCLUSION

This report is to alert the medical community to the need for careful hepatic function monitoring if using anti-

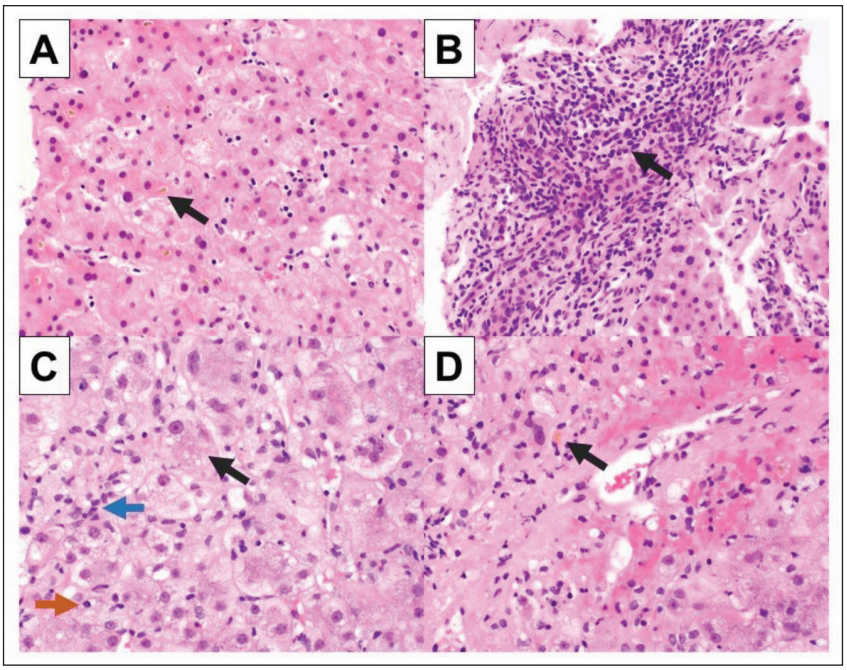

Fig. 3. Liver biopsy from patient 1 showed prominent canalicular cholestasis (*A*, arrow) and portal tract lymphocytic infiltrates (*B*, arrow). There was no significant hepatocyte ballooning or rosetting. Plasma cells and eosinophils were inconspicuous. The findings were most consistent with drug-induced liver injury. Liver biopsy from patient 2 (*C*) showed hepatocyte swelling, ballooning, clustering, microvesicular steatosis (black arrow), scattered apoptotic bodies (orange arrow), and mild lymphocytic infiltrates in the lobules (blue arrow). Zone 3 necrosis with hepatocyte dropout was evident and there was mild cholestasis (*D*, arrow). All images are stained with hematoxylin and eosin with original magnification at ×400.

PD-1 inhibitors simultaneously with azole antifungals. Further study in their combination effects are needed. Furthermore, we would strongly advise against concomitant therapy with KTZ and PD-1 inhibitors to treat hypercortisolism and recommend an alternative steroid inhibitor such as metyrapone or a glucocorticoid receptor blocker.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

REFERENCES

1. **Tang J, Yu JX, Hubbard-Lucey VM, Neftelinov ST, Hodge JP, Lin Y.** Trial watch: the clinical trial landscape for PD1/PDL1 immune checkpoint inhibitors. *Nat Rev Drug Discov*. 2018;17:854-855.
2. **Mota JM, Sousa LG, Braghiroli MI, et al.** Pembrolizumab for metastatic adrenocortical carcinoma with high mutational burden: two case reports. *Medicine (Baltimore)*. 2018;97:e13517.
3. **Lin AL, Jonsson P, Tabar V, et al.** Marked response of a hypermutated ACTH-secreting pituitary carcinoma to Ipilimumab and Nivolumab. *J Clin Endocrinol Metab*. 2018;103:3925-3930.
4. **Castinetti F, Guignat L, Giraud P, et al.** Ketoconazole in Cushing's disease: is it worth a try? *J Clin Endocrinol Metab*. 2014;99:1623-1630.
5. **Yan JY, Nie XL, Tao QM, Zhan SY, Zhang YD.** Ketoconazole associated hepatotoxicity: a systematic review and meta-analysis. *Biomed Environ Sci*. 2013;26:605-610.
6. **U.S. Food and Drug Administration.** FDA Drug Safety Communication: FDA limits usage of Nizoral (ketoconazole) oral tablets due to potentially fatal liver injury and risk of drug interactions and adrenal gland problems. Available at: https://www.fda.gov/drugs/drugsafety/ucm362415.htm. Accessed August 26, 2020.
7. **De Velasco G, Je Y, Bossé D, et al.** Comprehensive meta-analysis of key immune-related adverse events from CTLA-4 and PD-1/PD-L1 inhibitors in cancer patients. *Cancer Immunol Res*. 2017;5:312-318.
8. **Zhang X, Ran Y, Wang K, Zhu Y, Li J.** Incidence and risk of hepatic toxicities with PD-1 inhibitors in cancer patients: a meta-analysis. *Drug Des Devel Ther*. 2016;10:3153-3161.
9. **Casey RT, Giger O, Seetho I, et al.** Rapid disease progression in a patient with mismatch repair-deficient and cortisol secreting adrenocortical carcinoma treated with pembrolizumab. *Semin Oncol*. 2018;45:151-155.
10. **Alsaab HO, Sau S, Alzhrani R, et al.** PD-1 and PD-L1 checkpoint signaling inhibition for cancer immunotherapy: mechanism, combinations, and clinical outcome. *Front Pharmacol*. 2017;8:561.
11. **Desai VC, Cavanaugh TM, Kelton CM, Guo JJ, Heaton PC.** Trends in the utilization of, spending on, and prices for outpatient antifungal agents in US Medicaid programs: 1991-2009. *Clin Ther*. 2012;34:2118-2131.
12. **Del Castillo M, Romero FA, Argüello E, Kyi C, Postow MA, Redelman-Sidi G.** The spectrum of serious infections among patients receiving immune checkpoint blockade for the treatment of melanoma. *Clin Infect Dis*. 2016;63:1490-1493.