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Liver Allograft Failure After Nivolumab Treatment—A Case Report With Systematic Literature Research

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Background. Orthotopic liver transplantation (OLT) is a potential curative treatment in patients with hepatocellular carcinoma (HCC); however, treatment options for recurrent HCC after OLT are limited. Immune checkpoint inhibitors, such as nivolumab, an inhibitor of programmed cell death protein 1, have been successfully used for metastatic HCC but data on safety of nivolumab following solid organ transplantation are limited. **Methods.** We report a 53-year-old woman with HCC who was treated with OLT. After 2 years, HCC recurred. Initial treatment with sorafenib was discontinued due to side effects and disease progression. Progressive HCC in the lung and lymph nodes was subsequently treated with nivolumab. One week after the first nivolumab dose, rapid progressive liver dysfunction was noted. Liver biopsy revealed severe cellular graft rejection prompting treatment with intravenous steroids and tacrolimus. Liver function continued to decline, leading to severe coagulopathy. The patient succumbed to intracranial hemorrhage. **Results.** A systematic PubMed search revealed 29 cases treated with a checkpoint inhibitor following solid organ transplantation. Loss of graft was described in 4 (36%) of 11 cases with OLT and in 7 (54%) of 13 cases after kidney transplantation. However, cases with favorable outcome were also described. Eighteen cases with adverse events were identified upon searching the World Health Organization database VigiBase, including 2 cases with fatal outcome in liver transplant recipients due to graft loss. **Conclusion.** Experience with checkpoint inhibitors in solid organ transplant recipients is limited. Published cases so far suggest severe risks for graft loss as high as 36% to 54%.

(*Transplantation Direct* 2018;4: e376; doi: 10.1097/TXD.0000000000000814. Published online 20 July, 2018.)

Hepatocellular carcinoma (HCC) frequently occurs in patients with liver cirrhosis. In selected cases, orthotopic liver transplantation (OLT) is the best curative option.

Hepatocellular carcinoma recurs in about 16%[1,2] of patients after OLT. If OLT is not an option, therapeutic options for HCC recurrence include the tyrosine kinase inhibitor

TABLE 1.

Summary of solid organ transplant recipients treated with checkpoint inhibitors

Age	Sex	Organ transplanted/years after transplantation	Immune-suppression (at time of checkpoint inhibitor treatment)	Cancer	Checkpoint inhibitor/No. doses	Outcome for graft	Pathology of graft	Treatment of graft rejection	Outcome for cancer	Overall outcome/time after start therapy	References
67	3M	Liver/8 y	Rapamycin, 1 mg/d	Melanoma	Ipilimumab, 4×	No rejection	Mild hepatitis	None	Regression	Alive at 3 mo	Morales et al[11]
59	F	Liver/8 y	Tacrolimus	Melanoma	Ipilimumab, 4×	No rejection	No rejection	n/a	Progression	Alive at 9 mo	Ranganath et al[12]
67	F	Liver/1.5 y	Prednisolon, 10 mg	Melanoma (liver metastases before transplantation)	Ipilimumab, 1×	Rejection	Acute rejection	High-dose steroids, MMF, Sirolimus restarted	Progression	Death at 4 mo	Dueland et al[13]
62	F	Liver/5 y	Prednisone, sirolimus, 1 mg/d MMF	MPNST-like Melanoma	Ipilimumab, 4× Pembrolizumab, 4× as 2nd line	No rejection	n/a	n/a	Progressive disease after ipilimumab Partial response after Pembrolizumab	Alive at 24 mo	Kuo et al[14]
20	M	Liver/3 y	Sirolimus	HCC	Nivolumab, 2×	Loss of function	Cellular/ab-mediated rejection	Prednisone[a] + IVIG	n/a	Death at 5 wk	Friend et al[15]
14	M	Liver/3 y	Tacrolimus	HCC	Nivolumab, 1×	Loss of function	Cellular/antibody-mediated rejection	Prednisone[a]	n/a	Death at 4 wk	Friend et al[15]
53	F	Liver/3 y	Everolimus	HCC	Nivolumab, 1×	Loss of function	Cellular rejection	Methylprednisolone 500 mg/d for 5 days, after prednisone 40 mg Tacrolimus	Progressive disease	Death at 4 wk	The current case: Gassmann et al
41	M	Liver/1 y	Tacrolimus	HCC	Nivolumab, 15×	No rejection	n/a	n/a	Progression	Death >7 mo	De Toni et al[16]
54	M	Liver/13 y	Tacrolimus, everolimus, prednisone	Squamous non–small-cell lung cancer	Nivolumab, 3×	No rejection	n/a	n/a	Progression	Death at 15 mo	Biondani et al[17]
57	M	Liver/4 y	Tacrolimus, MMF, steroids + rapamycin-inhibitor	HCC	Pembrolizumab, 10× (Sorafenib)	No rejection	n/a	n/a	Complete radiological resolution	No adverse events, alive at 10 mo	Rammohan et al[18]
35	M	Liver/20 y	Tacrolimus	Melanoma (IIC)	Pembrolizumab, 2×	No rejection	Diffuse hepatocellular injury with hydropic degeneration, reactivation of HCV infection	Pulse doses of intravenous methylprednisolone, oral steroid taper ledipasvir-sofosbuvir	No evidence of melanoma >6 months after stopping pembrolizumab	Alive at 6 mo	Schwartsman et al[19]
58	M	Kidney/8 y	Prednisone, 5 mg mg/d	Melanoma	Ipilimumab, 4×	No rejection	No rejection	n/a	First partial response, later progression	Alive at 19 wk	Lipson et al[20]
40	M	Kidney (2nd)/16 y	Prednisolone, 5 mg/d	Melanoma	Ipilimumab, 2×	Loss of function	Acute cellular-mediated rejection	High-dose methylprednisolone	Melanoma progression	Death (n/a)	Jose et al[21]
72	M	Kidney/11 y	Prednisone, 5 mg/d	Melanoma	Ipilimumab, 14 mo	No rejection	No rejection	n/a	Partial response	Alive at 14 mo	Lipson et al[20]
77	M	Kidney/8 y	Tacrolimus prednisone, 5 mg/d	Melanoma	Ipilimumab, 3× Nivolumab, 7×	No rejection	No rejection	n/a	Progressive disease	No adverse events, survival n/a	Herz et al[22]
72	M	Kidney/4 y	No immunosuppression with start ipilimumab/nivolumab	Spindle-cell cutaneous SCC	Ipilimumab and Nivolumab, 4×	Loss of function	n/a	Methylprednisolone	Complete response	Dialysis, death at 5 mo	Miller et al[23]
48	M	Kidney/14 y	Prednisolone, 5 mg/d	Melanoma	Ipilimumab, 2×	Loss of function	Acute cellular rejection BANFF 2a	High-dose steroids	Disease control	Dialysis, alive at 34 wk	Spain et al[24]
70	M	Kidney/6 y	Sirolimus, prednisone 40-10 mg tapering scheme	Adenocarcinoma of the duodenum	Nivolumab, 1× + 6×	No rejection	No rejection	n/a	Regression	No adverse events, alive at 7 mo	Barnett et al[25]

Age	Sex	Organ/duration	Immunosuppression	Cancer	Checkpoint inhibitor	Loss of function	Rejection BANFF	Steroid treatment	Response	Outcome	Reference
74	M	Kidney/3 y	Cyclosporine, prednisone[a]	NSCLC	Nivolumab, 3×	Loss of function	2b	Prednisone[a]	n/a	Dialysis, survival n/a	Bolis et al[26]
69	F	Kidney/14 y	Sirolimus, prednisone, 5 mg/d	SCC	Nivolumab, 11×	No rejection	No rejection	n/a	Regression	Pneumonitis, survival n/a	Kittai et al[27]
60	F	Kidney/13 y	MMF, prednisolone	Melanoma	Nivolumab, 4×	No rejection	n/a	n/a	Melanoma progression	Death at 1 mo	Winkler et al[28]
63	F	Kidney/12 y	Prednisone, 10 mg/d	Melanoma	Nivolumab, n/a	Loss of function	n/a	Methylprednisolone, 500 mg/d	Response in lung metastases, stable disease	Dialysis, alive at 8 mo	Ong et al[29]
55	M	Kidney (2nd) 32 y	Cyclosporine	Melanoma	Pembrolizumab	No rejection		n/a	Melanoma progression	Death at 1.5 y	Winkler et al[28]
57	F	Kidney/25 y	Prednisone, 5 mg/d	Cutaneous SCC	Pembrolizumab	Loss of function	Cellular rejection	Glucocorticoids[a]	Regression	Dialysis, alive at 8 mo	Lipson et al[30]
58	M	Kidney/14 y	Azathioprin, everolimus	Melanoma	Pembrolizumab, 2×	Loss of function	No biopsy	n/a	Progression	Death at 1 mo	Kwatra et al[31]
69	F	Heart/15 y	Tacrolimus	Melanoma	Ipilimumab, 4×	No rejection	No rejection	n/a	Melanoma progression after several months	Death at 10 mo	Gastman et al[32]
49	M	Heart/19 y	Tacrolimus, sirolimus, prednisone[a]	SCC	Nivolumab, 1×	Loss of function	Cellular rejection Grade IIIa	Methylprednisolone	n/a	Death at 8 mo	Owonikoko et al[33]
72	F	Heart/10 y	Cyclosporine, MMF, prednisone[a]	NSCLC	Nivolumab, 21×	No rejection	No rejection	n/a	Stable disease after 8 months	No adverse events, alive at 8 mo	Kittai et al[27]
58	F	Cornea/1 y	No	NSCLC	Nivolumab, 9×	n/a	n/a	Methylprednisolone 500 mg/d for 3 days, after prednisone[a]	n/a	Transplant dysfunction, alive at 9 mo	Le Fournis et al[34]

[a] Dosage not available.

IVIG, intravenous immunoglobulin therapy; MPNST, malignant peripheral nerve sheath tumor; SCC, squamous cell carcinoma; n/a, not available; NSCLC, non–small-cell lung carcinoma; BANFF, Banff schema for grading liver allograft rejection.[35]

sorafenib.[3] Sorafenib has also been used for patients after OLT, but the therapeutic benefit has not been clearly established.[4] Usage of sorafenib is in addition limited due to severe side effects, including hand-foot syndrome, nausea, emesis and wasting in a large percentage of patients.[3,5]

Recently, checkpoint inhibitors have been introduced for immune activation in patients with metastatic cancer, resulting in tumor regression and even remission in a subgroup of patients.[6] Nivolumab, an inhibitor of programmed cell death protein 1 (PD-1), was successfully established as first or second line treatment in various malignancies, such as melanoma, squamous cell skin carcinoma, non–small-cell lung carcinoma, kidney carcinoma, and classical Hodgkin lymphoma.[7] Case series also demonstrate benefits of nivolumab in HCC on an off-label basis.[8] However, solid organ transplant recipients were excluded from checkpoint inhibitor registration and there is limited experience with the application of nivolumab in this patient population.[9,10] We here present a case of fulminant liver transplant failure with cellular rejection and fatal outcome in a patient treated with nivolumab for recurrent HCC.

MATERIALS AND METHODS

Patient's relatives provided written informed consent to publication.

We performed a systematic Pubmed literature search with the following complementary search strategies (February 22, 2018): (nivolumab OR ipilimumab OR pembrolizumab OR atezolizumab) AND (transplantation OR transplant OR rejection) yielding 210 publications; (pd-1 AND checkpoint inhibitor) AND (organ transplant recipient OR transplantation) yielding 53 publications; Immune checkpoint inhibitor AND liver transplant yielding 13 publications. All identified publications were screened and redundant reports were excluded. Publications describing patients after solid organ transplantation treated with 1 or a combination of the 4 checkpoint inhibitors, nivolumab, ipilimumab, pembrolizumab, or atezolizumab with sufficient information regarding the outcome for the transplanted organ were included. Altogether, our literature research identified 25 publications with 29 cases. The final list is provided in Table 1.

We searched for individual case safety reports (ICSRs) in the World Health Organization (WHO) global database VigiBase. In this database, spontaneously reported adverse drug reactions are collected as ICSR. We included all ICSRs with the substances, nivolumab, ipilimumab, pembrolizumab, or atezolizumab and the reactions "transplant rejection", "graft rejection" as a preferred term, low-level term or high-level term reported in the database until August 6, 2017 (total number of ICSRs 15160.275). Matching of patients from VigiBase to case reports in Table 1 was not possible and potentially redundant cases could not be excluded.

Case Presentation

A 53-year-old woman of central African origin received domino-liver transplantation 36 months ago for HCC that developed on the basis of liver cirrhosis due to chronic hepatitis C. Immunosuppression after OLT included prednisone for 3 months on a tapering scheme, mycophenolate mofetil (MMF) 1 to 2 g/d for 3 months and everolimus 1 mg/d. In 4 posttransplant biopsies within the first 5 months no rejection was shown. Hepatitis C virus was successfully treated

**ALT, AST, bilirubin, AFP and INR before and after Nivolumab**
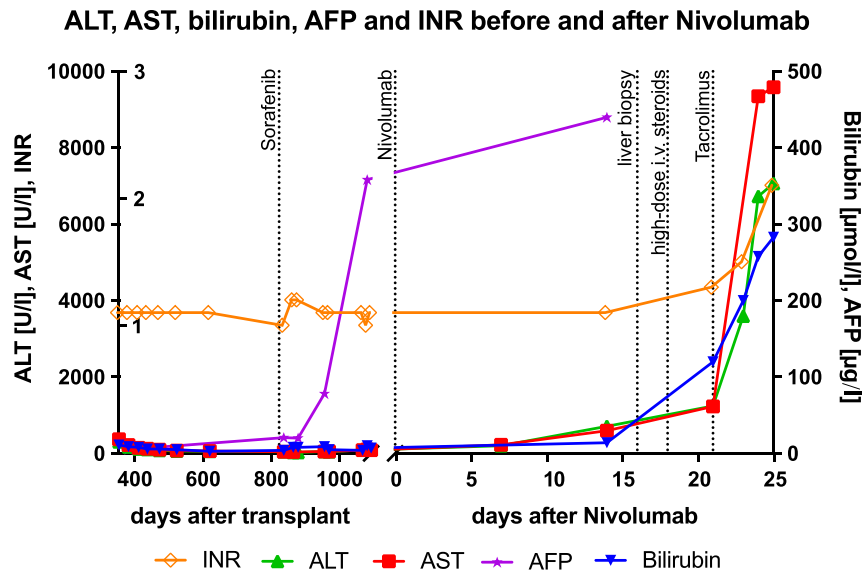
FIGURE 1. Time course for liver function tests and tumor markers before and after nivolumab treatment.

with sofosbuvir 400 mg/ledipasvir 90 mg for 12 weeks. Two years after OLT, HCC recurred with pulmonary, pulmonary bihilar and retroperitoneal lymph node metastases. The patient received sorafenib for 2 months but stopped the treatment due to intolerable nausea, emesis, and tumor progression. No hepatic recurrences could be detected. After thorough discussion of benefits and potential adverse drug reactions—including risk of graft loss and fatal outcome—treatment with nivolumab was initiated. A change of immune suppression was not performed because a recent randomized controlled study failed to show survival benefits upon sirolimus treatment for patients with HCC treated after transplantation.[36] After administration of a single dose of 200 mg nivolumab (3 mg/kg body weight), an increase in liver function tests was noted 1 week after administration (Figure 1). Liver biopsy was performed 2 weeks after administration of nivolumab and demonstrated acute cellular transplant Rejection Activity Index (RAI) 7 (Figure 2) under immunosuppression with everolimus (trough level, 3.3 μg/L) and MMF. Intravenous high-dose steroid therapy (methylprednisolone 500 mg daily) for 5 days was administered but liver function tests continued to increase. Steroids were changed to prednisone 40 mg per day orally and tacrolimus 6 mg per day (aiming for a trough level of 5 μg/L) was added. No antiplatelet agent and only prophylactic anticoagulation with subcutaneous low molecular weight heparin was used.

Over the next 3 days, the patient's condition continued to deteriorate with tiredness, severe nausea and emesis, diffuse upper abdominal pain, night sweats, alcoholic stools, dark urine, scleral icterus but no signs of neurological dysfunction. The patient was admitted to the hospital. Laboratory tests revealed a rapid increasing of liver enzymes (aspartate aminotransferase, 9347 U/L; norm, <35 U/L; alanine aminotransferase, 6730 U/L; norm, <35 U/L), signs of coagulopathy (international normalized ratio, 2.1; norm, <1.2; factor V, 28%; norm, 50-150%), acute renal dysfunction (creatinine, 190 μmol/L; norm, 44-80 μmol/L), most likely due to dehydration, secondary to vomiting. Therapeutic levels of everolimus (3.3 μg/L) and tacrolimus (5.1 μg/L) were documented. Tests for viral infections, including CMV, hepatitis B, C, and E, were

negative; diagnostic tests for HSV and autoimmune hepatitis were not performed due to low pretest probability. We noted a low-level Epstein-Barr virus viremia of 2323 IE/mL (detection limit, <122 IE/mL); however, similar levels have been noted before on several occasions after OLT. Ultrasound confirmed regular blood supply to the liver. Acetylcystein treatment and encephalopathy prophylaxis with rifaximine and lactulose were started.

On the second day of admission, the patient suddenly lost consciousness (Glasgow coma scale, 3), prompting transfer to the intensive care unit and intubation. Computed tomography scan demonstrated extensive liver necrosis and intracerebral bleeding with signs of increased cerebral pressure (Figure 3). After discussion with her family, therapy was discontinued and the patient passed away on the same day, 25 days after first administration of nivolumab.
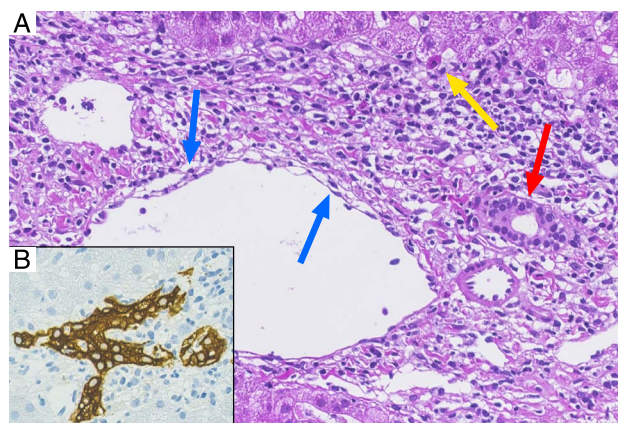
FIGURE 2. Liver biopsy 16 days after nivolumab. A, HE staining illustrating prominent portal mixed inflammation with interface activity and isolated hepatocyte necrosis (yellow arrow), cytoplasmatic vacuolization of the duct epithelium consistent with bile duct damage (red arrow) and subendothelial lymphocytic inflammation with lifting up of the endothelium compatible with endothelitis (blue arrow); 400×. B, Cytokeratin-7 immunohistochemical staining highlighting the influx of inflammatory cells in the ductal epithelium associated with dysmorphic changes of the bile duct (magnification, 400×).

FIGURE 3. Abdominal imaging. A, Contrast-enhanced CT scan demonstrating an enlarged lymph node in the liver hilum (arrow) due to HCC recurrence 27 months after liver transplantation. B, CT scan 9 months later with stable lymph node before nivolumab treatment 35 months after liver transplantation. C, CT scan at the day of death 25 days after nivolumab treatment with inhomogeneous hypodense areas in the right hepatic lobe (arrows) suggestive for parenchymal necrosis. No signs of intrahepatic HCC recurrence. CT, computed tomography.

Systematic Literature Search

Our systematic literature research for the use of checkpoint inhibitors in solid organ recipients revealed 25 articles describing 29 patients, including our presented case (Table 1, for search strategy see methods). Fourteen of 29 cases were kidney transplant recipients, 11 cases were liver transplant recipients, 3 were heart transplant recipients, and 1 patient had received cornea transplantation.

Graft loss was defined as severe transplant dysfunction resulting in death in patients after liver or heart transplantation and hemodialysis in patients after kidney transplantation, respectively. Because in all patients uncontrolled neoplasia was present, retransplantation has not been an option. Acute rejection was defined graft dysfunction reversed by adequate medical therapy (1 case by Dueland et al).

Rates of graft loss are reported according to the checkpoint inhibitor used; patients receiving combination therapies are considered for both drugs.

Nivolumab Treatment in Transplant Patients

Loss of transplant function after nivolumab administration alone or in combination with ipilimumab[15-17,22-29,33,34] occurred in 9 (56%) of 16 cases: graft loss was observed in 4 of 8 cases of kidney transplant recipients, in 3 of 5 cases of liver transplant recipients and 1 of 2 cases after heart transplantation. In the case of cornea transplant nivolumab resulted in graft dysfunction.

Overall cancer response is known in only 11 of the 16 cases: in 5 cases, progressive disease was described; in 3 cases, regression was reported; and in 3 cases, stable disease was reported.

Ipilimumab Treatment in Transplant Patients

Loss of transplant function after ipilimumab administration alone or in combination with nivolumab or pembrolizumab[11-14,20-24,32] occurred in 4 (36%) of 11 cases: ipilimumab administration after kidney transplant resulted in graft loss in 3 out of 6 cases and in liver transplant recipients in 1 of 4 cases. One heart transplanted patient showed no rejection after ipilimumab.

Cancer response was reported in all cases: in 7 of 11 cases progressive disease was described, 1 case showed stable disease and 3 cases showed tumor regression.

Pembrolizumab Treatment in Transplant Patients

Loss of transplant function after pembrolizumab administration alone or in combination with ipilimumab[14,18,19,28,30,31]

occurred in 2 (33%) of 6 cases: pembrolizumab resulted in graft loss in 2 of 3 cases of kidney transplant recipients but in no rejection in 3 cases after liver transplantation.

Cancer response was reported in all cases: in 2 of 6 cases, progressive disease was described, the remaining 4 cases showed cancer regression.

A search in VigiBase, the WHO database for pharmacovigilance, revealed worldwide 9 ICSRs of transplant rejection after using the checkpoint inhibitor nivolumab between 2015 and August 2017. Transplant rejections of the kidney (n = 6), cornea (n = 1), or without organ specification (n = 2) were reported. In all cases, nivolumab was labeled as the suspected drug. In 1 patient, the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor ipilimumab was coadministered. Fatal outcome was documented in 1 female patient with nivolumab treatment for liver carcinoma, who died after transplant rejection. Further details are not provided in the database.

DISCUSSION

We report a single case of fatal liver failure 3 weeks after administration of a single dose of nivolumab in a patient with recurrent HCC 2 years after liver transplantation. Our systematic literature search identified additional cases with graft loss after checkpoint inhibitor treatment. Overall, graft loss or acute rejection, as discussed above, was described in 13 (45%) of 29 cases across all checkpoint inhibitors. For nivolumab, ipilimumab, and pembrolizumab, rejection rates of 56%, 36%, and 33%, respectively, were apparent. Loss of graft function for liver allografts occurred in 3 (37%) of 11 cases, for kidney allografts in 7 (50%) of 14 cases, and heart allografts in 1 (33%) of 3 cases.

Therefore, our data suggest a severe risk of transplant rejection after use of checkpoint inhibitors in patients after solid organ transplantation. Even though the rates of rejection were highest with nivolumab, our data do not allow to compare relative risks of 1 checkpoint inhibitor versus the other. Furthermore, because our study relies on publication of case reports, the possibility of publication bias has to be considered which might result in overestimation or underestimation of rejection rates.

The safety of nivolumab or other checkpoint inhibitors in solid organ recipients has not been established because this patient population was excluded from relevant clinical trials.[9,10] Formal assessment of causality of nivolumab exposure and fatal liver transplant rejection in our case suggests a

"probable" relationship according to the WHO/Council for International Organizations of Medical Sciences criteria.[37] Chronological order of drug exposure and adverse event, existence of additional cases with nivolumab treatment and graft rejection, pharmacological plausibility, and exclusion of other nonpharmacological explanations suggest a causal relationship between nivolumab treatment and graft rejection.

Immune checkpoint inhibitors, including nivolumab and ipilimumab, revolutionized the treatment of various malignancies. Nivolumab (Opdivo) is a human monoclonal IgG4 antibody which blocks PD-1 receptor on activated T cells, B cells, natural killer T cells, monocytes, and dendritic cells.[38] Programmed cell death protein 1 receptor has 2 ligands, PD-L1 and PD-L2, which are expressed on tumor cells and antigen-presenting cells in tumor microenvironment. Binding of the receptor with its ligand (programmed cell death 1 ligand 1 [PD-L1]) leads to negative regulation of T cells and lack of T cell response. Therefore, prevention of PD1 and PD-L1 interaction by nivolumab can restore T cell–mediated tumor suppression.[26] The mechanism of ipilimumab (Yervoy) is different from nivolumab because ipilimumab inhibits CTLA-4 activity. Generally, CTLA-4 modulates T-cell activation during the initial phase of the immune response, whereas PD-1 acts during the effector phase.

Induction of immune tolerance of organ-transplanted patients is crucial after solid organ transplantation. Both PD-1 and CTLA-4 signaling pathways contribute to immune tolerance of transplanted organ. PD-L1 expression was proposed to be the key component of graft tolerance after liver transplantation, because higher expression provides a negative feedback, creating a protective shield from human T-cell responses.[39] Additionally, PD-1 plays a crucial role in both induction and maintenance of peripheral transplant tolerance by its ability to alter the balance between pathogenic and regulatory T cells and it is also involved in T-cell exhaustion— another emerging mechanism in transplant tolerance.[40-44]

On the other hand, blocking CTLA-4 in early phases after transplantation led to transplant rejection in a murine model, whereas late blockade seems not to affect transplant survival.[45,46]

Therefore, inhibition of either CTLA-4 or PD-1 after solid organ transplantation might trigger immune-mediated organ failure. However, which checkpoint inhibitor would be more favorable in organ transplant recipients remains unclear. It also remains unclear whether the time passed after transplantation before checkpoint inhibitor treatment might decrease the risk for graft loss.

Patients with and without organ failure did not significantly differ regarding age, time after transplantation, sex, graft (liver/kidney/heart) and treatment with nivolumab, ipilimumab, or pembrolizumab. We noticed a minor trend for more organ failure in younger patients, which failed to reach statistical significance.

Our case and the 2 cases described by Friend et al are remarkable for an extreme severity of liver transplant rejection leading to rapid transplant failure, nonresponsive to 5 days high-dose steroids. Hepatic side effects of nivolumab are frequent also in patients without OLT, and immune-mediated hepatitis with a median time to onset of 3.3 months (range, 6 days to 9 months) is the main hepatic adverse effect of nivolumab. However, nivolumab-induced hepatitis typically resolves after discontinuation of treatment[47] and usually begins much later than 16 days after administration as in our patient. It has different histologic features than described in the liver biopsy in our patient, as it is characterized by an acute lobular hepatitis with isolated or confluent necrosis and a predominantly lymphocytic infiltrate. In contrast, in our case, portal tract inflammation was dominated by a mixed infiltrate with interface activity, bile duct injury and endothelitis compatible with acute cellular rejection (RAI: 3/2/2 = 7). Taken together, nivolumab-induced hepatitis seems an unlikely explanation for liver failure in our patient, and histological changes favor an acute cellular rejection (Figure 2).

However, the clinical course in our patient also remains highly unusual for an acute cellular rejection because this complication only infrequently occurs more than 1 year after transplantation, especially in patients with good therapeutic adherence and no prior history of cellular rejection. Further, acute cellular rejection typically responds to steroid treatment and virtually never progresses to fulminant liver failure. It therefore seems probable that nivolumab exposure and PD-1 inhibition had induced a cellular rejection of unusual severity, leading to fulminant liver transplant failure. However, the underlying immunological mechanisms are unknown.

Our patient ultimately succumbed to fatal intracranial bleeding. Whether this complication is related to coagulopathy associated with liver failure remains unclear because permission to perform autopsy in this patient was not granted.

Management of checkpoint inhibitor-associated solid allograft failure is unclear. Acute graft rejection resolves upon high-dose steroid treatment in 70% to 80% of all cases.[48] However, neither in our patient nor in those patients described by Friend et al or in other cases identified in our literature search did high-dose steroid treatment result in clinical improvement. Rapid clinical deterioration in our patient precluded alternative treatment options, such as infliximab,[49] antithymoglobuline,[50] or cyclosporine. Plasmapheresis was not used in the cases described involving organ failure after checkpoint inhibitor treatment. Plasmapheresis has been used for treatment of acute humoral rejection after OLT[51] but it will likely not stop the T cell–mediated immune rejection after checkpoint inhibitor treatment. However, plasmapheresis would remove the checkpoint inhibitor from the circulation, which might potentially be beneficial. Taken together, no medical treatment for graft failure after checkpoint inhibitor treatment has been identified.

CONCLUSIONS

Solid allograft failure is a severe or catastrophic complication after checkpoint inhibitor treatment. No medical treatment options have been identified. Our case and several published cases suggest a 36% to 54% risk of graft loss on checkpoint inhibitor treatment.

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