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Tumor regression concomitant with steroid-refractory GVHD highlights the pitfalls of PD-1 blockade following allogeneic hematopoietic stem cell transplantation

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For Hodgkin lymphoma (HL) patients who fail frontline therapy, salvage regimens including autologous and allogeneic hematopoietic stem cell transplant (alloHSCT) may cure select patients, although relapse remains a significant cause of transplant failure. Treatment strategies aimed at bolstering posttransplant immunity to both prevent and treat relapse following alloHSCT are of significant interest, especially immune checkpoint inhibitors such as cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and programmed death 1 (PD-1) monoclonal antibodies.

Programmed death ligand 1 (PD-L1) binds to its cognate receptor, PD-1, found on activated T-cells resulting in suppression of T-cell activation and proliferation. Classical Hodgkin lymphoma (cHL) is characterized by tumor-infiltrating T-cells expressing PD-1 while surrounding malignant Reed-Sternberg (RS) cells.[1] RS cells constitutively express PD-L1, although amplification of chromosome 9p24.1 and its induction by JAK2 results in increased expression.[2,3] Blockade of the PD-L1/PD-1 pathway restores antitumor activity of CD4+ HL-infiltrating T-cells and IFN-γ production.[1] The PD-1 inhibitor, nivolumab, initially showed remarkable efficacy with an overall response rate (ORR) of 87% in a phase 1 study of heavily pretreated relapsed/refractory HL patients, excluding allotransplant patients.[4] The ongoing phase 2 study of nivolumab in HL patients who failed to respond to autologous HSCT and brentuximab recently reported an ORR of greater than 66% and recent use of pembrolizumab phase I data in similar patients revealed an ORR of 65%.[5,6] These studies excluded allotransplant recipients bed upon evidence that prior murine models demonstrated mice subjected to PD-1/PD-L1 blockade developed rapid, lethal acute GVHD (aGVHD).[7]

At present, few reports exist in the literature of relapsed HL patients receiving PD-1 checkpoint inhibitors following an alloHSCT. [8–12] Notably, none of the patients who received PD-1 inhibitors in these studies were reported to have active GVHD at the time of PD-1 inhibitor administration nor were any receiving systemic immunosuppression. Remarkably, patients had substantial disease regression ranging from partial to complete

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responses. Of note, two deaths from steroid-refractory GVHD have been reported in allogeneic transplant recipients following the administration of pembrolizumab (n=1) and nivolumab (n=1).[11,12]

Davids et al. recently published results from a phase1/1b study using ipilimumab in patients with relapsed hematologic malignancies after alloHSCT, excluding patients on any immunosuppression at time of treatment.[7] Four of 28 patients treated on this study developed exacerbations of GVHD but all responded to steroids.[7] Three of four of these patients were then precluded from further ipilimumab administration.[7] To our knowledge, there have been no reports of patients with active cGVHD treated with checkpoint inhibitors nor any reports of patients treated with PD-1 inhibitors developing steroid-refractory GVHD that were treated successfully. Here, we report both on such a patient.

A heavily pretreated female with refractory HL underwent a reduced-intensity conditioning matched related alloHSCT. She received a donor lymphocyte infusion five months after alloHSCT due to falling donor T-cell chimerism which was associated with the subsequent development of moderate skin, and oral cGVHD and and severe liver cGVHD per NIH consensus criteria. Despite ultimately achieving 100% donor chimerism in myeloid and T-cell lineages, her disease progressed at eight months after alloHSCT for which she was treated with repeated cycles of brentuximab. Initially, her disease responded to this agent but with progressive cycles she developed worsening odynophagia with biopsy-confirmed oral and esophageal GVHD which resolved with high-dose steroids. After 13 cycles of brentuximab, she eventually developed brentuximab-refractory disease and subsequently received palliative combination chemotherapy which proved ineffective. Her disease progressed in less than one month following cessation of palliative chemotherapy.

She was counseled on the risks and benefits of off-label use of nivolumab. At the time of nivolumab administration, she was receiving prednisone 10mg daily for active oral GVHD evidenced by persistent mucositis, ulceration, and pain. Reduced-dose nivolumab was administered on day 0 (0.5mg/kg) and day 14 (1mg/kg). Approximately 3 weeks after initiating nivolumab, she developed rising transaminases, significant mucositis and dysphagia. Biopsies of the esophagus and liver were consistent with GVHD. Of note, circulating numbers of CD4+ and CD8+ T-cells increased in association with her cGVHD flare (Figure 1). Methylprednisolone 1mg/kg daily was initiated for three days but without any improvement, therefore the dose was increased to 2mg/kg for 5 days resulting in some minimal resolution of her mucositis. When her steroid dose was decreased to 1.5mg/kg/day she had an acute rise in her transaminases and significant worsening of her cutaneous GVHD prompting dose-escalation of steroids to 2mg/kg. Given GVHD persistence in the context of high-dose steroid use, she was diagnosed with steroid-refractory GVHD (SR-GVHD). Based upon prior data demonstrating a high response rate to SR-GVHD[14], she received combined monoclonal antibodies targeting IL-2 and TNF-α (basiliximab, an interleukin-2 (IL-2) receptor monoclonal antibody, and infliximab, a tumor necrosis factor alpha (TNF-α) monoclonal antibody)which resulted in rapid resolution of GVHD (Figure 1). Imaging studies were notable for a dramatic reduction in disease burden (Figure 2, Panel A-I). She sustained a partial response for 5 months following nivolumab therapy with complete resolution of GVHD. She subsequently developed disease progression, was treated

with nivolumab at a dose of 0.5mg/kg for 3 cycles with a good partial tumor response, but she again developed liver and oral GVHD requiring retreatment with dual cytokine blocking monoclonal antibodies. At present she survives with resolution of her GHVD.

Given the recent report of ipilimumab being used successfully to treat disease relapse following alloHSCT, the use of checkpoint inhibitors after alloHSCT to treat relapsed disease, as well as the development of GVHD following such therapy will likely increase. As observed in this case, small doses of nivolumab to induce PD-1 blockade resulted in a severe flare of cGVHD which was steroid-refractory, but which fortunately could be rapidly curtailed with dual anti-cytokine therapy. Importantly, although the patient had a dramatic regression of treatment refractory HL, this case highlights the risks associated with using immune checkpoint modulation in alloHSCT patients, especially in those with active cGVHD, even if it is only mild in nature as was the case with the patient described herein.

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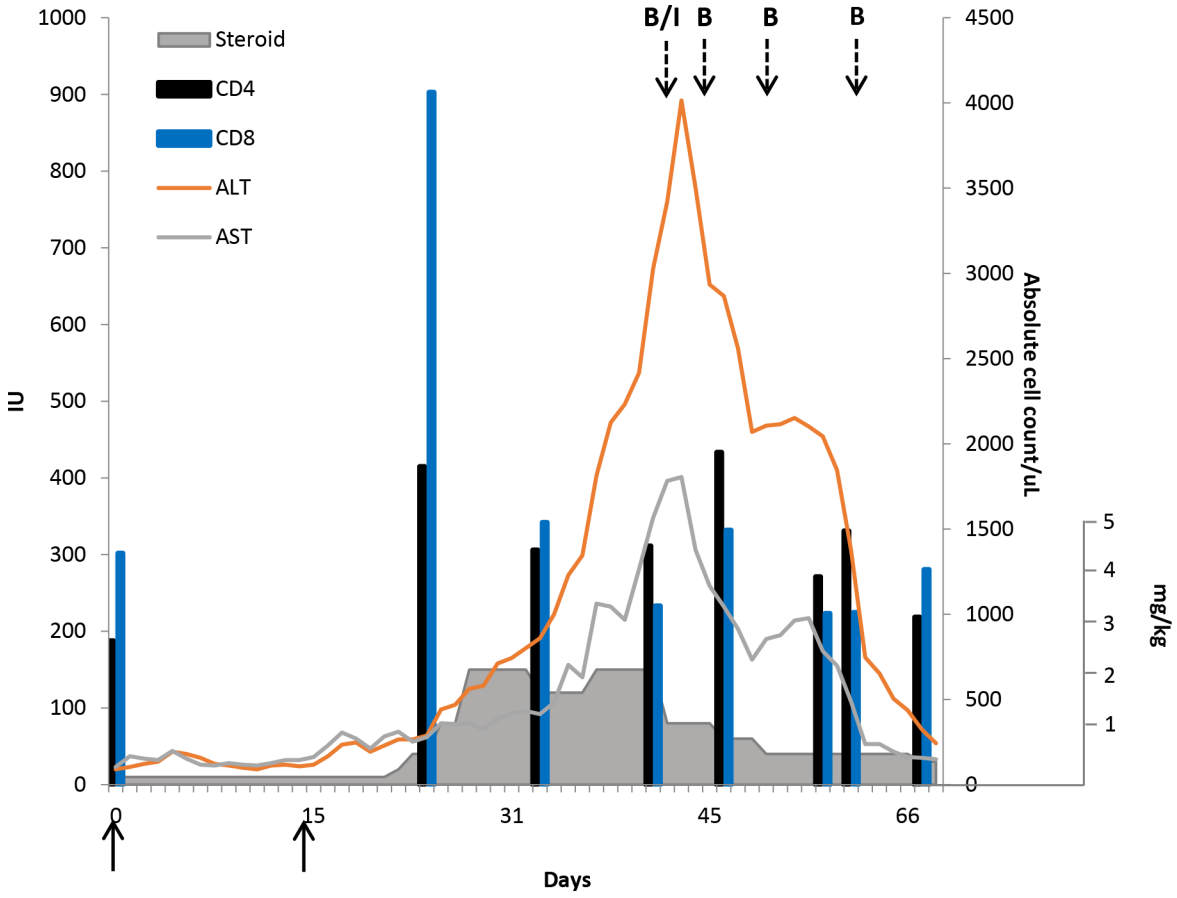

Figure 1.

Evidence of graft versus host disease post-nivolumab inhibition. Nivolumab 0.5mg/kg was administered on day 0 (*solid arrow*) and 1mg/kg on day 14 (*solid arrow)*. Liver enzymes, ALT (*red*) and AST (*green*) rise following nivolumab administration. Notable elevations of CD8 (*blue*) and CD4 (*black*) also occurred following administration of nivolumab. Steroid (i.e. methylprednisolone) doses are shown. Basiliximab and infliximab (*B/I*) were administered with subsequent basiliximab (*B*) doses given.

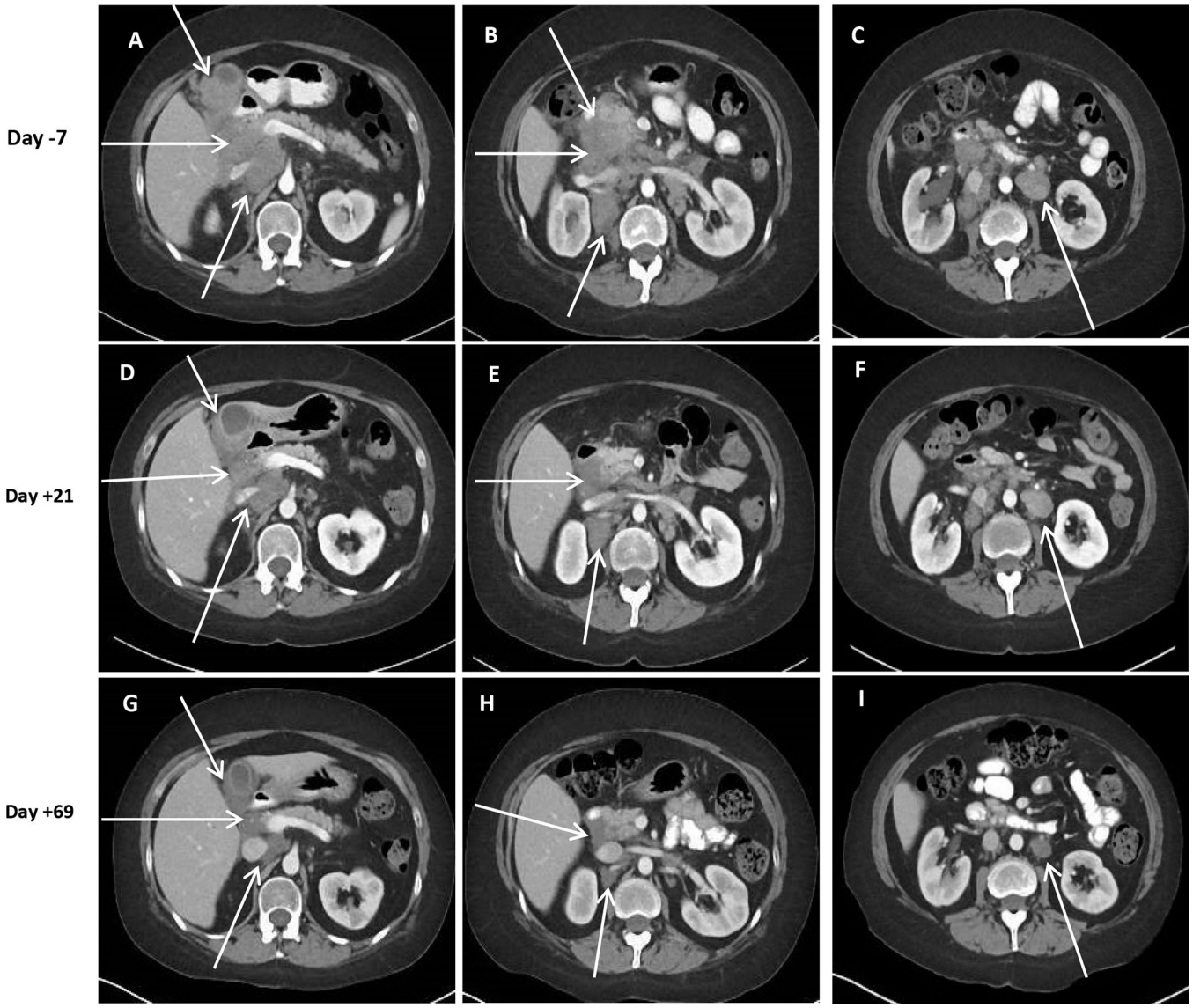

Figure 2.

Panels A-C: CT images obtained 7 days prior to nivolumab therapy showing relapsed Hodgkin's disease. **Panels D-F:** CT images obtained 21 days after initiation of nivolumab. **Panels G-I:** CT images obtained 69 days after initiation of nivolumab.