INNOVATIONS JOURNALS

Case Report

Histiocytic Sarcoma Treated with Pembrolizumab: A Case Report and Literature Review

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ABSTRACT

Histiocytic sarcoma (HS) is a rare hematologic malignancy that has historically been treated with lymphoma-based regimens with a median survival of 6 months. We describe a case of a 51-year-old woman who presented with acute back pain and cord compression. She was diagnosed with HS with diffuse skeletal lesions and high expression of programmed death ligand 1 (PD-L1). She was subsequently treated with chemotherapy plus off-label use of pembrolizumab followed by allogeneic stem cell transplantation. Ultimately, the patient died in the setting of progression of disease 17 months after her stem cell transplantation and 26 months after her diagnosis. This article also presents a literature review of cases of HS treated with programmed death ligand inhibition.

Keywords: case report, histiocytic sarcoma, PD-L1 inhibitors

INTRODUCTION

Histiocytic sarcoma (HS) is a rare and aggressive hematopoietic neoplasm. The name is a misnomer: it is not a "sarcoma" because it is derived from monocyte/macrophage lineage. It is diagnosed by morphologic features as well as the presence and absence of many immunohistochemical markers. The National Cancer Database reported only 409 histologically confirmed cases between 2004 and 2015.[1] The disease can present in a unifocal or multifocal pattern; given the lack of data, multifocal disease has no consensus guidelines for treatment and thus has historically been treated with lymphoma-based regimens with a median overall survival of 6 months.[1,2] However, molecular profiling has lead to many new immunologic treatments for both common and orphan hematologic diseases like HS (see Table 1).[3–6] In this report we detail the treatment course of a patient treated with pembrolizumab, as well as a literature review of other case reports of HS treated with programmed death ligand 1 (PD-L1) inhibitors. This case report is written according to CARE guidelines. The patient provided consent to publish this case report. Approval by the local ethics committee is not required for case reports deemed not to constitute research at our institution.

CASE REPORT

A 51-year-old woman with no relevant past medical and no family history of hematologic malignancies presented to the emergency department with a 4-week history of progressively worsening back pain and acute onset of difficulty walking. She underwent magnetic resonance imaging of her spine that revealed osteoblastic lesions involving T7–T8 and T12–L2 with an epidural thoracic mass causing cord compression. Computed tomography (CT) of the chest as well as abdomen pelvis demonstrated diffuse axial and appendicular skeletal lesions and a 3.2 × 3.8 × 2.5–cm soft tissue mass within the right gluteal musculature. She

Table 1. Immunologic therapies for hematologic malignancies

Type of Agent	Cell Target	Agent	FDA-Approved Indication	Year Approved
Monoclonal antibody/checkpoint inhibitor	CD20	Rituximab	NHL	1997
			CLL	
		Ofatumumab	CLL	2009
		Obinutuzumab	CLL	2013
			FL	2016
	CD52	Alemtuzumab	CLL	2007
	CD38	Daratumumab	MM	2013
	SLAMF7	Elotuzumab	MM	2014
	PD-L1	Pembroluzimab	HL	2017
		PMBCL	2018	
		Nivolumab	HL	2016
	CCR4	Mogamulizumab	CTCL	2018
Bispecific T-cell engagers ("BiTE therapy")	CD19 and CD3	Blinatumomab	ALL	2018
	CD20 and CD3	Mosunetuzmab	FL	2022
		Epcoritamab	DLBCL	2023
Antibody-drug conjugates	CD30	Brentuximab vedotin	HL	2011
			ALCL	2011
			CTCL	2017
			PTCL	2018
Chimeric antigen receptor T-cell therapy	CD19	Tisagenlecleucel	ALL	2017
			DLBCL	2018
			FL	2021
		Axicabtagene ciloleucel	DLBCL	2017
			tFL	
			PMBCL	
			HGBCL	
		Brexucabtagene autoleucel	MCL	2020
		Lisocabtagene maraleucel	DLBCL	2021
			HGBCL	
			PMBCL	
			FL	
	BCMA	Idecabtagene vicleucel	MM	2021
		Ciltacabtagene	MM	2022

Information collected from FDA.gov/drugs (last accessed July 20, 2023).
ALCL: anaplastic large cell lymphoma; ALL: acute lymphocytic leukemia; BCMA: b-cell maturation antigen; CLL: chronic lymphocytic leukemia; CTCL: cutaneous T-cell lymphoma; DLBCL: diffuse large b-cell lymphoma; FDA: US Food and Drug Administration; FL: follicular lymphoma; HGBCL: high-grade B-cell lymphoma; HL: Hodgkin lymphoma; MCL: mantle cell lymphoma; MM: multiple myeloma; NHL: non-Hodgkin lymphoma; PD-L1: programmed death ligand 1; PMBCL: primary mediastinal B-cell lymphoma; PTCL: peripheral T-cell lymphoma; tFL: transformed follicular lymphoma.

underwent successful T6–T8 decompression and excisional mass biopsy followed by palliative radiotherapy to her spine at T6–T9 and T12–L3 with resolution of neuromuscular weakness and back pain.

Analysis of the biopsy demonstrated HS. Immunohistochemical studies returned positive results for CD4, CD163, as well as variable positivity for CD68 and negativity for MPO, lysozyme, CD1a, CD15, CD21, S100, pancytokeratin, Oscar cytokeratin, CK5/6, GATA3, TTF1, p40, PAX8, ER, SOX10, and WT1. The tissue demonstrated wild-type *BRAF* and 70% PD-L1 expression by immunohistochemistry at our institution. The PD-L1 test was performed with a Ventana Medical Systems platform with an SP263 antibody clone and scored with percentage of tumor cells (TCs) with any membranous staining. Subsequent molecular testing revealed microsatellite stability, low tumor mutation burden, and PD-L1 95%. This molecular study was performed through a commercially available platform (Caris Life Sciences) with an SP142 antibody clone and used TC scoring. There were also pathogenic mutations in *SDHB* and *TP53*. Histologic examination showed sarcomatoid malignant neoplasm with anaplastic nuclei and brisk mitotic activity including atypical forms (Fig. 1).

Bone marrow biopsy demonstrated markedly hypocellular bone marrow (2%) with trilineage hypoplasia but no evidence of HS. A fluorodeoxyglucose–positron emission tomography CT (FDG PET-CT) scan revealed multiple hypermetabolic masses in the spleen, pancreatic head, right gluteus maximus muscle, many lumbar vertebrae, and the pelvis. Within 2 weeks of her initial surgery, the patient developed an obstructive hyperbilirubinemia secondary to a rapidly growing 2.6 × 3.7–cm pancreatic mass obstructing her common pancreatic and bile ducts for which she underwent an endoscopic retrograde cholangiopancreatography with stenting for decompression.

Shortly afterwards, she received palliative radiotherapy to her spine at T6–T9 and T12–L3. After a discussion with

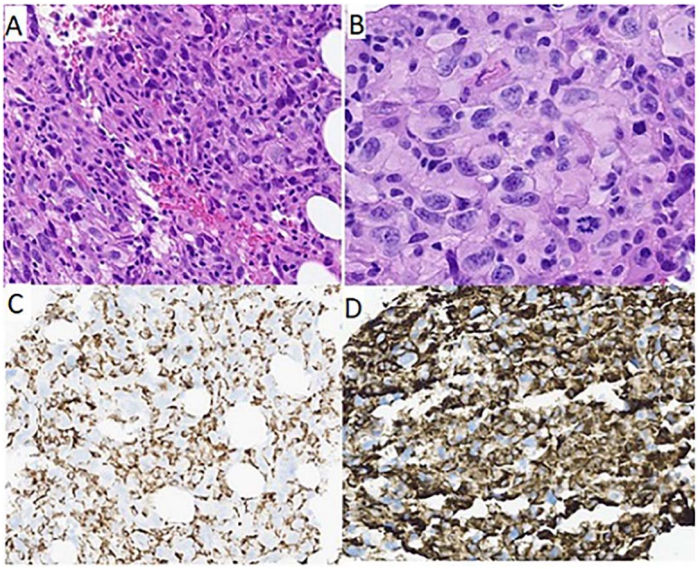

Figure 1. Pathology from initial biopsy. (A) High magnification of neoplastic cells replacing bone marrow (40×). (B) Sarcomatoid malignant neoplasm replacing marrow with atypical mitotic figure present. (C) Positive immunohistochemical CD68 staining. (D) Positive immunohistochemical CD163 staining.

the patient of the benefits and risks of standard chemotherapy, she started systemic therapy with cyclophosphamide 750 mg/m^2 (dose reduced for biliary dysfunction), doxorubicin 50 mg/m^2, vincristine capped at 1 mg, and prednisone at 100 mg for 5 days (CHOP chemotherapy) plus pembrolizumab 200 mg. Her cerebrospinal fluid was negative for malignancy, and she received one dose of intrathecal methotrexate 10 mg/m^2 for central nervous system prophylaxis. Pembrolizumab was held during cycles 2–4 owing to insurance denial and then approved for compassionate use and restarted with cycle 5. Her interim PET-CT scan after cycle 3 showed a near complete response to treatment; however, PET-CT following cycle 6 was concerning for increased FDG avidity in the left upper quadrant of the abdomen, right lower quadrant of the abdomen, and bone marrow uptake at the right proximal femur (Fig. 2). A repeated bone marrow biopsy was normocellular and remained negative for HS involvement, and biopsy of the right lower abdominal mass revealed adipose and fibrous tissue with no viable tumor. Owing to clinical and radiographic suspicion of progression, she was treated with second-line ifosfamide 5000 mg/m^2, carboplatin with targeted area under the curve of 5 mg/min/mL, etoposide 100 mg/m^2 (ICE chemotherapy) with pembrolizumab 200 mg for two cycles. Posttreatment PET-CT again indicated concern for increasing FDG avidity; however, biopsy of a perisplenic mass revealed histiocytic infiltrate with necrosis. The decision was made to pursue consolidation with allogeneic stem cell transplant (SCT). She received two cycles of bridging clofarabine monotherapy with subsequent PET-CT that demonstrated improvement in the abdominal masses but increased FDG uptake of her distal right femoral bone.

She received 2000 cGy of radiation to the right femoral bone and then transitioned to SCT with busulfan and fludarabine conditioning around 10 months after her initial diagnosis. Her first 100 days after SCT were complicated by gram-positive bacteremia, febrile neutropenia, and colonic graft-versus-host disease. On transplant day 100, her bone marrow biopsy revealed no evidence of disease

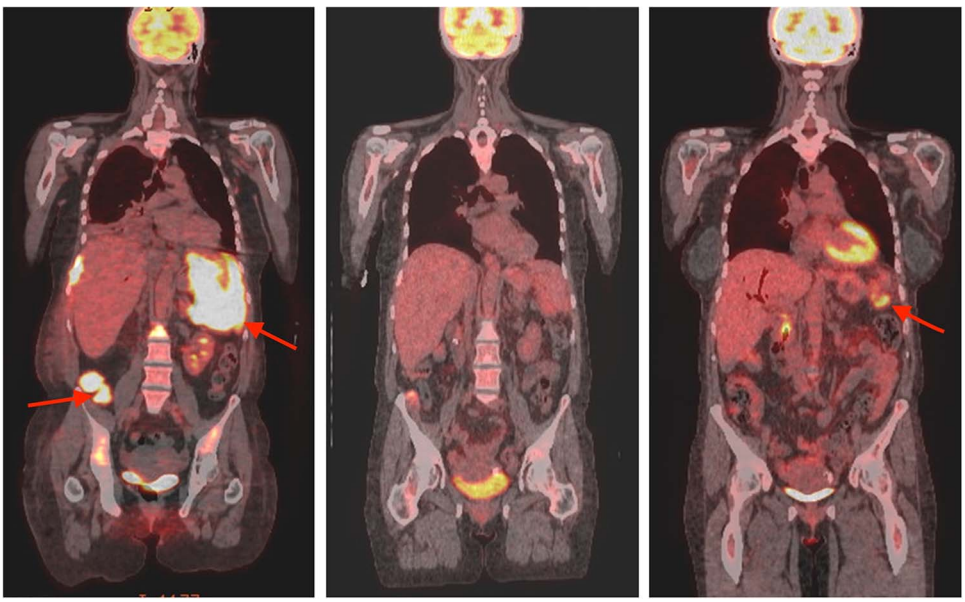

Figure 2. PET-CT scans showing response to CHOP and pembrolizumab. From left to right are three PET-CT scans: left, prior to treatment with CHOP and pembrolizumab; middle, after cycle 3; and right, after cycle 6. Initial PET-CT scan is notable for a conglomerate of hypermetabolic nodules in perisplenic space, adjacent to the liver, and multiple bone lesions (red arrows). Middle PET-CT scan demonstrates marked decrease in all lesions. Right PET-CT scan is notable for recurrent hypermetabolic lesion in left upper quadrant (red arrow). CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; PET-CT: positron emission tomography–computed tomography.

Table 2. Cases of patients treated with PD-L1 inhibitors

Case	Age, years	Sex	Localization	Treatment	PD-L1 Positivity	Best Response to PD-L1 Inhibitor	Survival	Author
1	17	F	Pulmonary, axial bone, appendicular bone, multiple lymph nodes	AALL0434 protocol (PD) > modified ALCL99 regimen (PR) > cladribine-cytarabine > nivolumab	75%	Partial	Survived at least 6 months after nivolumab	Bose et al[13]
2	66	M	Ileum, liver, abdomen, mediastinal adenopathies	CHOP > ICE > alemtuzumab (PD) trametinib > imatinib > nivolumab > lenalidomide	15–20%	Progression of disease	Died 20 months after diagnosis	Voruz et al[14,15]
3	60s	F	Adenopathy in mediastinal, peritracheal, hilar, left paracardiac lymph nodes	Doxorubicin > trametinib > nivolumab	90%	Partial	Survived at least 1 year post diagnosis	Campedel et al[16]
4	43	F	Left femoral bone, right occipital bone, lung nodules, intrapelvic lymph nodes	CHOP > cladribine-cytarabine > radiation > nivolumab	"Strongly positive"	Partial	Survived at least 18 months after diagnosis	Imataki et al[12]
5	51	F	Epidural tissue, axial bone, appendicular bone, right gluteal area	CHOP + pembrolizumab > ICE + pembrolizumab > SCT	70–95%	Unclear, possibly partial	Survived 26 months after diagnosis	Huff et al (current case)

Based on information from Branco et al.[10]
CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; ICE: ifosfamide, carboplatin, and etoposide; PD: progression of disease; PD-L1: programmed death ligand 1; PR: partial response; SCT: stem cell transplant.

and 100% donor DNA. Four months after her SCT, a repeated PET-CT demonstrated an area of increased uptake in her right gluteal area, biopsy proven as HS, for which she subsequently received 2000 cGy of radiation. Follow-up imaging demonstrated progression of disease and she started palliative therapy. She died 17 months after her SCT and 26 months after diagnosis.

DISCUSSION

Given its rarity, HS is poorly understood, challenging to diagnose, and has no standardized treatments. It is pathologically defined by its lack of distinctive features aside from histiocytic cell markers like CD163, CD68, and lysozyme.[7] The pathophysiology of histiocytic neoplasms is characterized by the accumulation of macrophage or dendritic-like cells infiltrating tissues, leading to an intense inflammatory reaction.[8] Recent studies have begun to elucidate their molecular biology profile by showing mutations in the RAS/MAPK pathway, leading to uncontrolled cell proliferation; those with BRAFV6000 mutations are highly sensitive to BRAF or MEK inhibition.[9] This has been borne out in case reports of HS treated with MEK inhibition as well.[9,10] Furthermore, like normal histiocytes, most of these malignancies express PD-L1/L2.[11]

There are several case reports targeting PD-L1 in patients with HS (Table 2).[12–16] Imataki et al[12] treated a 43-year-old woman with 12 cycles of nivolumab and, following resection of her primary femoral lesion, the patient had a complete response. Bose et al[13] used nivolumab to treat a 17-year-old woman with HS displaying 75% PD-L1 expression, after treatment with multiple lines of chemotherapy had failed. Like our case, they noted that an early PET-CT scan showed signs of progression with improvement on repeated imaging, raising the question of pseudoprogression. The other cases listed, including this one, had more moderate responses. Although information from these reports is limited, it appears all patients survived for more than 6 months following treatment with PD-L1 inhibitors. The successful use of individual BRAF, MEK, or PD-L1 inhibitors for HS echoes recent trials with these agents for melanoma, subsequently explored in combinatorial doublets or triplets in clinic trials. For example, this triple therapy for melanoma is thought to have a synergistic effect, as the MEK and BRAF inhibitors increase PD-L1 expression, although questions remain regarding the best clinical scenario for implementation.[17,18] This raises the question of whether HS, in a patient with the appropriate molecular profile, would respond to combination therapy with these agents despite potential risk of increase toxicity.

The limitations of this report are that it presents a single case with an off-label use of pembrolizumab for a rare and poorly understood malignancy. This patient's outcome may have been similar with or without the use of a checkpoint inhibitor given her youth and prior allotransplant. Adding a checkpoint inhibitor also has significant costs and potential toxicities. Furthermore, pembrolizumab was also held during the initial few weeks so the patient

probably did not receive full potential therapeutic benefits. Lastly, based on the biopsies early in her treatment course, it is clear there was not a complete response after starting pembrolizumab.

In summary, we present a case of a patient with metastatic HS with high expression of PD-L1 who underwent a complex treatment regimen including an allogenic SCT and pembrolizumab.

In the past 2 decades, a deeper understanding of the molecular mechanisms that drive HS has resulted in new treatment modalities targeting MEK and BRAF. Owing to the high expression of PD-L1, testing the checkpoint inhibitors in rare diseases such as HS may be reasonable options to consider in future clinical trials.

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