

Application of PD-L1 blockade in refractory histiocytic sarcoma: A case report

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Received April 29, 2022; Accepted June 22, 2022

DOI: 10.3892/mco.2022.2569

Abstract. Histiocytic sarcoma (HS) is a rare hematological malignancy, which exhibits morphological and immunophenotypic features of histiocytes. A standard therapy for HS has not yet been established due to its rareness; therefore, disease control is not always possible. A multimodal treatment strategy has been suggested for HS. The present study reported on a case of a 43-year-old female patient who complained of left femoral pain, which was caused by left femoral bone mass. A biopsy of their left femoral bone tumor revealed that the patient had HS. Their sarcoma was localized in the femoral bone and was not considered to be curable, due to local infiltration of the bone tumor beyond the periosteum. The patient then underwent two types of HS-specific chemotherapy; however, both regimens were ineffective. As a result, they underwent radiation therapy at the sites of progressive disease. Because the HS cells of the patient expressed PD-L1, they were treated with nivolumab (240 mg/body, biweekly) for residual diseases in the right occipital bone, multiple lung nodules, intrapelvic right lymph node and primary site. Nivolumab treatment resulted in a complete response at all sites, with the exception of the primary site, which was confirmed by ¹⁸F-fluorodeoxyglucose-positron emission tomography/computed tomography. The patient received additional nivolumab treatment as consolidation therapy for 1 year. In addition, residual disease of the femoral head was completely resected. The surgically resected refractory tumor revealed the tumor cells no longer pathologically expressed PD-L1. In conclusion, for refractory and recurrent HS in which surgical resection is not appropriate, treatment with immune-checkpoint inhibitors, such as nivolumab, may be considered an optional but promising immunotherapy if the tumor histologically expresses PD-L1. The present study detected one of the refractory mechanisms of ICI treatment.

Introduction

Histiocytic sarcoma (HS) is a rare hematological malignancy with an unknown prevalence (1). The etiology of HS is being researched; however, HS cells exhibit an immunophenotypically mature histiocyte phenotype. In the WHO classification (2017) (1), HS is classified as histiocytic and dendritic cell neoplasms (2,3). HS typically involves extranodal sites. The intestine, skin, and soft tissue are the most common extranodal sites for HS (4). Clinical presentations of HS are variable, ranging from localized disease with solitary mass to metastatic diseases with dissemination. Patients with localized HS is substantially treated with surgical resection, which exerts relatively better survival. Metastatic or disseminated HS should be managed with multimodal combination therapy consisting of surgery, chemotherapy and radiotherapy, because no standard therapy had been established. Even by intensive treatment optimal outcome have not been warranted in advanced disease cases.

HS may be caused by pluripotent germ cells (5). Specific markers of HS are CD68 and CD163 as diagnostic criteria. These surface antigens are originally expressed in histiocytes (4). In addition of histiocytic markers, CD31, CD4 and CD45RO are expressed in HS. Besides identical molecular features appear clonally in HS. *BRAF* mutation V600E occasionally identified in HS cells. In such cases, *BRAF* inhibitor could be provide as a target therapy, although *BRAF* mutation is not detected as universal alteration in HS. Other target option is immune checkpoint protein which is recently developing in the field of oncology (5). PDL1/L2 can be expressed physiologically by histiocytes (6,7). As a result, HS is produced from histiocytes expressing PD-L1/L2 (6-8). Although the cell of origin of HS is unknown, it reserves the surface antigens of histiocytes such as B7-H1 (PD-L1) (6,7). Thus, an anti-PD-L1 immune checkpoint inhibitor, representative nivolumab is expected to be a promising treatment agent (5). Successful treatment of cancers with PD-1/PD-L1 blockade shows promising clinical outcomes, initially in melanoma and then in a variety of cancers such as lung cancer, renal cell carcinoma, and Hodgkin lymphoma. We experienced the case with metastatic HS treated with nivolumab and revealed a refractory site among the patient's diseases was proven in pathological evidence as one of resistant mechanisms.

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Key words: histiocytic sarcoma, PD-L1, immune-checkpoint inhibitor, nivolumab, resistance mechanism, ¹⁸F-FDG-PET

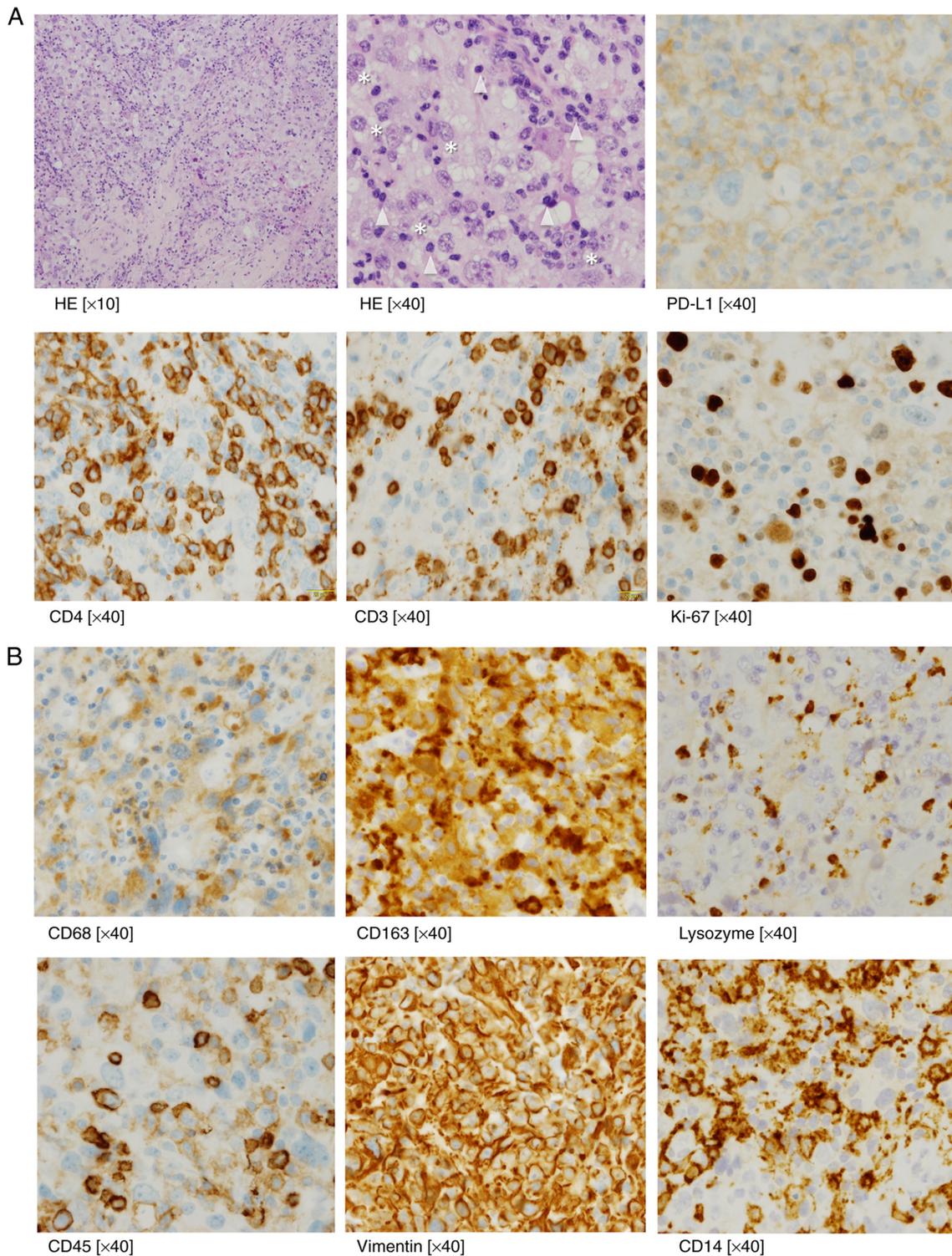


Figure 1. Pathological feature of HS. Pathology was used to diagnose the patient's bone biopsy. (A) HS tumor infiltrates cortical bone and is diffusely involved in the bone marrow. Histologic findings in the patient's first excisional biopsy H&E stain revealed atypical histiocytic proliferation with scattered large, hyperchromatic cells (indicated with asterisks), as well as small lymphocytes and eosinophils in the background. The PD-L1 stain (clone 28-8) was found to be positive in approximately 75% of the atypical cells. (B) The tumor cells were found to be positive for CD68 and CD163. Lysozyme stain was variable in its positivity in atypical cells. The tumor tissue was infiltrated by CD4⁺ T cells (indicated with small arrowheads). H&E, hematoxylin and eosin; HS, histiocytic sarcoma.

Case report

We treated a 43-year-old woman who had been diagnosed with HS; she was admitted to Kagawa University hospital (Miki, Japan) in May 2018. Her disease had been present for 3 months before

her diagnosis. Her initial symptom was left femoral pain, so she visited to the primary orthopedic clinic near her hometown. She was referred to our center, and an orthopedic surgeon performed a biopsy on her. A biopsy of the right iliac mass revealed atypical cell nodules with histiocytic immunophenotypes such as CD68⁺,

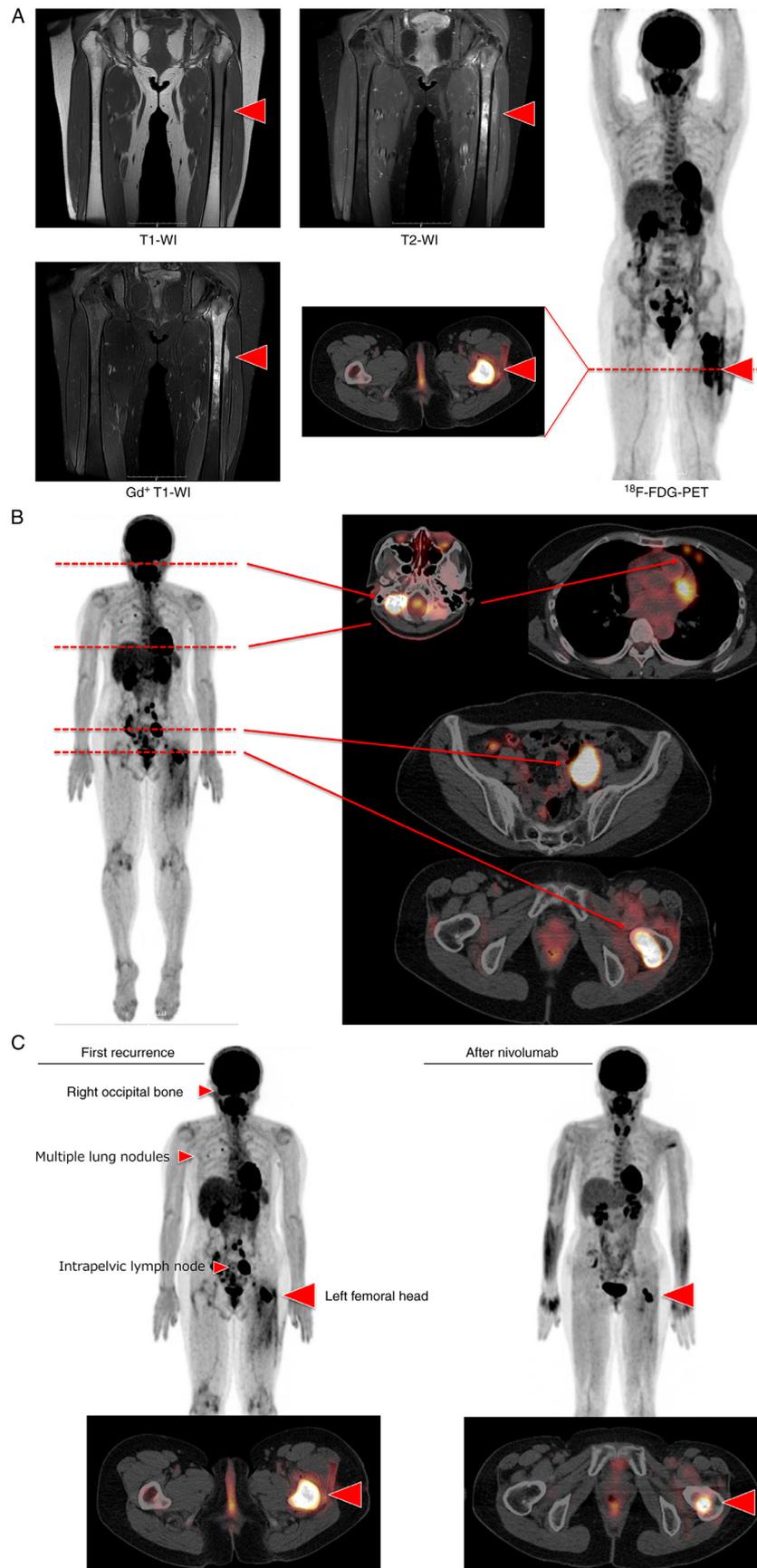


Figure 2. Imaging diagnosis of left femoral HS. (A) ¹⁸F-FDG-PET/CT study. The femoral lesion, which was diagnosed as HS, only ¹⁸F-FDG-PET/CT could detect. Left leg MRI was difficult to draw the tumor status is active or necrotic. (B) The patient recurred with new lesions; right occipital bone, multiple lung nodules, and intrapelvic right lymph node, and primary site; left femoral bone (left panel). (C) Imaging follow-up after radiation and nivolumab salvage therapy for recurrent HS. Following radiation therapy, FDG-PET/CT revealed a decrease in FDG accumulation in the right occipital bone and intrapelvic lymph node (right panel). Only after nivolumab therapy did the accumulation of multiple lung nodules disappeared completely and the left femoral head lesion diminished (right panel). ¹⁸F-FDG-PET/CT, ¹⁸F-fluorodeoxyglucose-positron emission tomography/computed tomography; HS, histiocytic sarcoma.

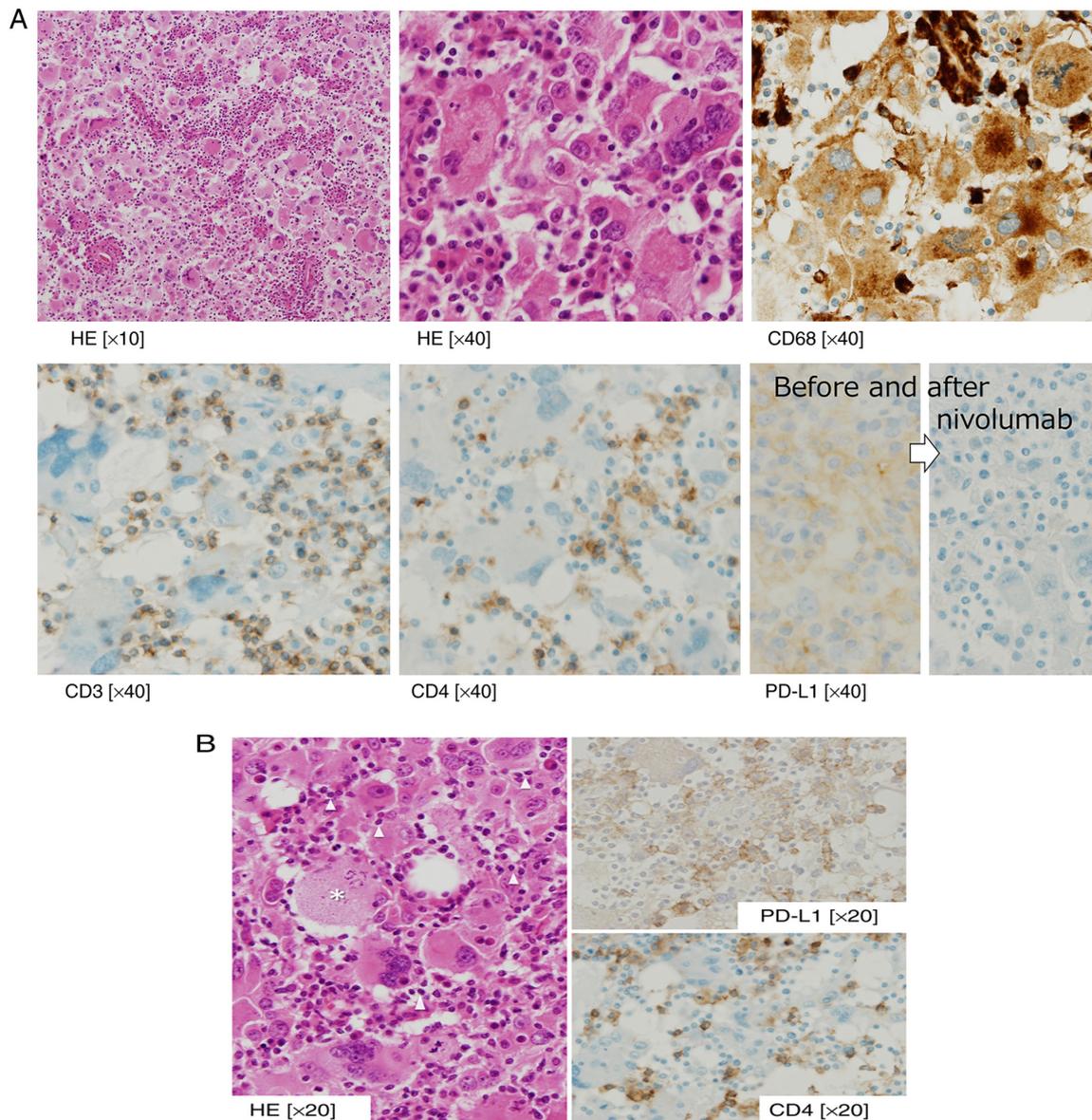


Figure 3. Pathological findings of relapsed and refractory primary lesions. After surgical resection of residual primary disease on the patient's left femoral head. (A) Tumor cells were shown as CD68 positive cells in the tissue (upper panels). CD4⁺ T cells infiltrated into interstitial tissues, however, PD-L1 (clone 28-8) was no longer positive on the tumor cells (0%) (lower panels). (B) Surrounding the alive tumor cells, many HS tumor cells still remain positive for PD-L1 antigen (right upper panel) and become apoptotic (left panel, asterisk) by the immunity of CD4⁺ T cells (left panel, shown by small arrowheads) (right lower panel). H&E, hematoxylin and eosin; HS, histiocytic sarcoma.

CD163⁺, lysozyme⁺, CD45⁺ (moderate), CD45RO⁺ (weak), vimentin⁺ (Fig. 1A and B), except for CD30. CD14 staining were weak in some of the large atypical cells (Fig. 1B), but not in CD34. In tumor cells, myeloid (myeloperoxidase), T cell (CD3, CD4, and CD8) and B cell (CD20) lineage markers were all negative. Follicular dendritic cell markers (CD1a and CD21) were negative. Other specific markers including SMA, desmin, S-100, AE1/AE3 were all negative. In the atypical cells, the Ki-67 proliferation index was 70%. These findings led to a diagnosis of metastatic HS. We also showed the infiltrating CD3⁺ CD4⁺ T cells as evidence of immune reaction (Fig. 1B).

Her disease was restricted to the left femoral bone, but it spread to the bone cortex and bone marrow (Fig. 2A). Initially, surgical resection was not recommended. We tried two chemotherapy regimens on her; CHOP (9) (cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisolone) and

cladribine-cytarabine (10). In a stable disease, neither cytotoxic chemotherapy regimen could reduce her tumor mass. We were looking for a method that would accurately assess treatment responses. Because chemotherapy was ineffective, the patient was treated with radiation therapy (RT) at the primary site on her left femoral bone. Thirty Gy of RT had been completed. Two months after RT, FDG-PET/CT depicted a clearance of FDG accumulation in the lesions including the left femoral head, which showed complete remission.

She succumbed to disease progression five months after being in remission. Right occipital bone, multiple lung nodules, intrapelvic right lymph node, and primary site were the recurrent disease sites (Fig. 2B). RT was administered to her lung nodules and primary site. Because pulmonary irradiation is toxic, and the primary site was already irradiated during the initial treatment. As a result, we investigated the BRAF V600E

mutation, the microsatellite instability (MSI) test, and the PD-L1 expression pathological sample at the onset. The first two tests came back negative, but PD-L1 was strongly positive in her HS tissue sample. As a result, we began administering nivolumab 200 mg biweekly. All metastatic lesions, including the lungs, were in remission after 12 cycles (Fig. 2C). Only a center lesion of the primary site were remained positive accumulation of FDG uptake (Fig. 2C). She underwent primary site resection and left femoral head replacement surgery. The pathological findings draw plenty of T cells within the tumor cells defect with PD-L1 antigen (Fig. 3A). This implicated HS tumor cells escaping from cell immunity. And in the area surrounding the residual tumor, HS tumor cells remain positive for PD-L1, in where HS was attacked and eliminated by active T cells (Fig. 3B).

Discussion

The clinical outcome of HS is unfavorable (11). So far, no standard chemotherapy has been reported. Multimodality treatment is important for treatment outcomes not only in cases of limited disease but also in cases of metastatic disease (12,13). Anecdotal evidence suggests that various treatable agents, such as CHOP, etoposide, and alkylating drugs, are available. Furthermore, novel approaches are being investigated, including thalidomide, alemtuzumab, vemurafenib, purine analogs, and vinblastine (12). A Mayo Clinic case report described a potential effect of RT in HS (8). After excluding patients with involvement of the bone marrow, spleen, or reticuloendothelial system, patients who were managed surgically had higher overall survival than those who were not (11). Finally, in the era of immune-oncology, an immune-checkpoint inhibitor brings a favorable response to this rare soft tissue sarcoma. Bose *et al* reported the first nivolumab is effective immunotherapy for HS and durable response in metastatic HS (14). Because HSs generally express the surface antigen PD-L1 (13), it is expected to respond well to immunotherapy (13). In our case, the tumor cells with PD-L1 were diminished with nivolumab, and the tumor cells defect PD-L1 escaped from the therapy with nivolumab. This resistant mechanism was proven in our case pathologically. Immunotherapy with PD-L1 and PD-1 antibodies could then be a novel and promising treatment option.

In literature reviews, a subset of patients with HS arises as a secondary neoplasm from hematological malignancies such as malignant lymphoma (4,12,13). In such cases, the underlying hematological disease is indolent, this subset of HS is considered a transformed or transdifferentiated (12). Lineage switching is used to explain this disease's trans-malignancy. Although there are no distinctive molecular markers for HS, some cases of trans-malignancy exhibit specific molecular genetic markers such as *BRAF* V600E (15) If this molecular marker is identified, it will be a target for *BRAF* inhibitors such as vemurafenib and dabrafenib (16). In our case, MSI was tested, but microsatellite instability-high status is rarely positive in HS. The hematological disease had not been mentioned in our case. The patient; however, was primarily resistant to cytotoxic agents such as the CHOP regimen. This intrinsic resistance

has yet to be identified. A significant proportion of sporadic HS patients have a B-cell genotype (17). More clinical research for novel agents to target HS is needed in this regard.

Some prognostic factors are known in this neoplasm (11,20,21). An epidemiological cohort study showed metastatic cases and secondary cases were independently poor prognostic factors (11,18). In this study, elevated LDH, ECOG PS 2-4, and Ann Arbor stage III-IV were independent risk factors (19). Without surgical treatment, stage IV disease has a poor prognosis (11). Multimodality combination therapy is a cornerstone of curative treatment (18). Following this, a chemotherapy-refractory case, such as ours, would have a poor prognosis. The pathogenesis or etiology of chemotherapy resistance, on the other hand, has not been investigated (20). Some molecular markers for treatment have been identified, primarily in activating driver mutations in the MAPK/ERK pathway (20-22). In some case reports, molecular target therapy, such as MEK inhibitors, trametinib, and vemurafenib, is highly effective in the treatment of recurrent/refractory HS (20,21). The efficacy of stem cell transplantation, including cell therapy, is being studied (23-25), and clinical results are anecdotal.

In conclusion, primary resistant or advanced HS can be safely treated with a PD-L1 antibody. Precision medicine policy plays an important role in this rare tumor. Treatable molecular targets should be screened for an efficient treatment procedure.

Acknowledgements

Not applicable.

Funding

This work was supported by JSPS KAKENHI (grant no. JP19K17927).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

OI and MU confirm the authenticity of all the raw data. OI managed the patient's case, contributed to the literature search and wrote the manuscript. HF and NK made substantial contributions to the conception and design of this report. MU analyzed the patient's data and suggested important intellectual content. HF, NK and MU took part in critical discussions. All authors read and approved the final manuscript.

Ethics approval and consent to participate

We obtained ethics approval from the Kagawa University Hospital Institutional Review Board (approval no. H23-023). This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Patient consent for publication

Written informed consent was obtained from the patient for publication of this study.

Competing interests

The authors declare that they have no competing interests.

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