Case Report

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Favorable outcome of a histiocytic sarcoma patient treated with immune checkpoint inhibitor: a case report

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Introduction and Importance: Histiocytic sarcoma (HS) is an extremely rare malignancy in which there has been no standard treatment approach. Some preclinical studies have provided rationales for the application of immunotherapy in advanced HS.
Case Presentation The authors reported a case of a 61-year-old patient with metastatic HS who had a rapid progression on ifosfamide, carboplatin, and etoposide chemotherapy. The authors performed PD-L1 testing, which showed a strong positivity in 90% of tumor cells. The patient was then treated with pembrolizumab 200 mg every 3 weeks. He refused palliative radiotherapy. A dramatic response in all sites was recorded on the PET-CT scan after three cycles. He was maintained on pembrolizumab, reaching over 30 months without disease progression.
Clinical Discussion Recent molecular data suggests there could be a role of immunotherapy in HS. In our patient, the disease was refractory to chemotherapy and pembrolizumab has been given based on the strong PD-L1 expression. Response to immunotherapy has also been recorded in several cases with malignant histiocytic neoplasm.
Conclusion Immunotherapy might bring sustained disease remission in PD-L1 high expression HS and further studies evaluating the role of immune checkpoint inhibitor in this disease are warranted.

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

Introduction

Histiocytic sarcoma (HS) is an extremely rare malignancy which accounts for less than 1% of all neoplasms of the hematopoietic system, with an incidence of only 0.17 per 1 000 000 individuals[1,2]. The tumor cells show morphologic and immunophenotypic features of mature histiocytes and are believed to arise from the monocyte/macrophage system[3]. Recent evidence suggests that HS can be primary or secondary following other hematolymphoid disorders such as low-grade B-cell lymphoma or leukemia[4].

This disease commonly presents in skin and connective tissue but can also manifest in other sites such as lymph nodes, respiratory, gastrointestinal, and nervous system[1]. There has been no standard treatment approach due to the rarity of the disease and the most popular therapy for advanced HS in previous reports was lymphoma-based chemotherapy protocols, but the efficacy was limited[3,5]. The median overall survival in a large-scale analysis was only 6 months[1]. Over the last decade, immune checkpoint inhibitors have shown significant efficacy in various hematological and solid tumors and have opened a new era in the field of oncology. Some recent studies demonstrated that HS cases could have strong PD-L1 (programmed death-ligand 1) expression[6], and based on the presumed origin from antigen presenting cells, immunotherapy can be a promising approach to treat this aggressive neoplasm. We hereby present a patient with widespread, PD-L1 high-expression HS who was successfully treated with Pembrolizumab and had a long-term response. This study has been reported in line with the (Surgical CAse REport) SCARE 2020 criteria[7].

HIGHLIGHTS

- Histiocytic sarcoma (HS) is an extremely rare malignancy in which there has been no standard treatment approach.
- Our patient with widespread, PD-L1 high expression HS was successfully treated with Pembrolizumab and had a long-term response.
- Immunotherapy might bring sustained disease remission in PD-L1 high expression HS and further studies evaluating the role of immune checkpoint inhibitor in this disease are warranted.

Case presentation

A 61-year-old male patient with no past medical histories and family histories was admitted to our hospital due to right shoulder pain and back pain for a few months. No history of

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injury was recorded. He had a good performance status and there were no palpable mass at the shoulder joint and no definite neurologic deficits. Shoulder joint MRI detected an abnormal contrast-enhanced mass of about 3 × 3 cm in size which was located near his right scapula and invaded the bone (Fig. 1). Blood tests showed mild anemia with a hemoglobin of 120 g/l, normal while blood count and normal liver, kidney function, and LDH (lactate dehydrogenase). The serum protein concentration was elevated with 84.3 g/l, in which the level of albumin and globulin were 38.7 g/l and 45.6 g/l, respectively. There was no evidence of monoclonal gammopathy in the free light chain test as well as the protein electrophoresis. A bone marrow biopsy was performed at a previous hospital which showed no abnormalities. The patient was also checked with a PET/CT scan, which showed a tumor at the corresponding position on the MRI with high FDG-uptake (SUV max of 12.0) and multiple FDG-avid lesions in the lungs, mediastinal lymph nodes and L4 vertebra. His PSA level was normal, and thyroid ultrasound, lower and lower gastrointestinal tract endoscopy showed no abnormalities. A core needle biopsy of the shoulder mass was obtained, which showed a nonspecific malignant tumor composed of diffuse, large cells with round or irregular nuclei, vesicle chromatin, prominent nucleoli and abundant, eosinophilic cytoplasm. The immunohistochemistry examination was positive with Vimentin, CD68, CD163, lysozyme, and negative with LCA (leukocyte common antigen), MPO (myeloperoxidase), CK (cytokeratin), and S100 (Fig. 2). Based on the clinical features and immunohistochemical findings above, the patient was diagnosed with advanced stage HS.

He was initially treated with an ICE chemotherapy regimen (ifosfamide, carboplatin, and etoposide). After two cycles, the pain worsened, mostly in the lumbar and right shoulder regions, and the patient could not lift his right hand. He also did not tolerate chemotherapy well. A re-evaluation PET/CT scan showed an increase in size and FDG-uptake level of the primary tumor (SUV max of 18.0) and metastatic lesions (Fig. 3). PD-L1 test was done to explore further treatment of immunotherapy, which showed a strong positivity in 90% of tumor cells. Due to the rapid progression on chemotherapy, we decided to start immunotherapy with pembrolizumab 200 mg every 3 weeks. Palliative radiation therapy to the right shoulder joint was also discussed with the patient but he refused radiotherapy. After three cycles of immunotherapy, the pain gradually decreased. PET/CT scan after three cycles found a very good response in all sites with a dramatic drop of the SUV max of bone lesions (Fig. 3). After six cycles of pembrolizumab, the patient achieved maximal remission in all lesions, in which no clear high FDG-uptake lesions were recorded on a PET-CT scan. The patient had pembrolizumab maintenance, reaching over 30 months without disease progression until now.

Discussions

HS, first described by Mathe in 1970[8], is a very rare neoplasm, and the diagnosis is usually made by exclusion of other tumors[3]. Differential diagnosis of HS might include lymphoma, metastatic carcinoma or melanoma, myeloid sarcoma, and Langerhans cell sarcoma[4,9]. Histological clues and judicious use of immunohistochemical markers help to confirm the diagnosis[4]. In our case, pathological interpretation was challenging because the majority of the biopsied tissue was necrotized. The small areas containing non-necrotic tumor showed some distinctive features, such as large cell with abundant eosinophilic cytoplasm, oval to irregular nuclei with predominant nucleoli suggesting a malignant tumor originating from mononuclear phagocytes or histiocytes. However, these morphological characteristics might be seen in a number of mimics[4,10]. Immunohistochemistry was therefore crucial for both confirming the final diagnosis and excluding the other possibilities. The expression with CD63, CD168, and Lysozyme was consistent with the immunophenotypic features of mature tissue histiocyte[4]. Meanwhile, due to the presence of some epithelioid tumoral cells, carcinoma should be a differential diagnosis. However, it was excluded by the absence of CK and the presence of Vimentin. Likewise, LCA staining limited to stroma infiltrating lymphocytes ruled out the potential of lymphoma. One of the myeloid cell markers, MPO, failed to express on the tumor. Due to the lack of reactive eosinophils and multinucleated giant cells on the H&E slide and negative S100 staining on the immunohistochemical slide, we did not consider

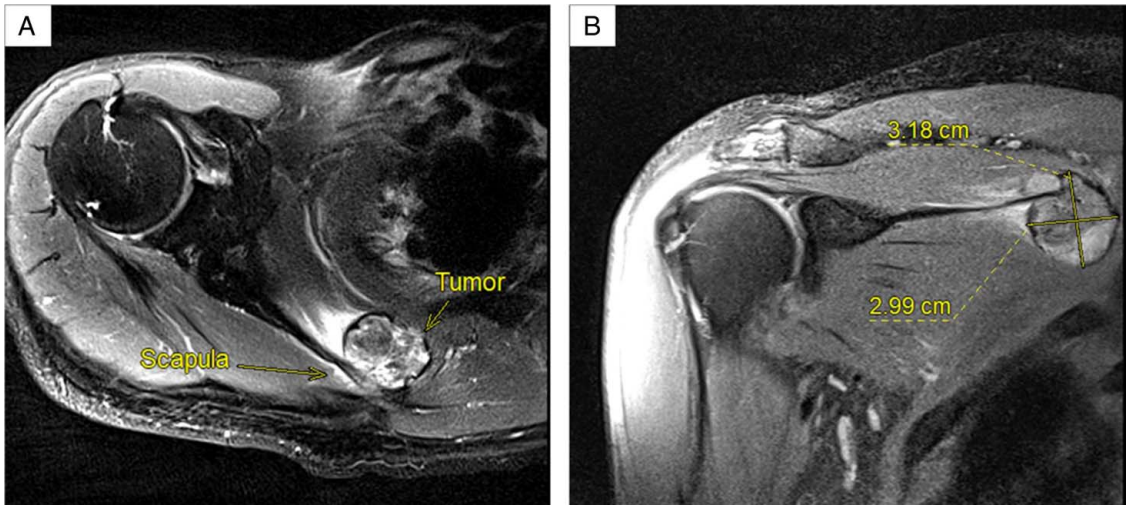

Figure 1. Pretreatment right shoulder MRI. The images showed a mass of 3 × 3 cm in size (B), with invasion of the scapula (A).

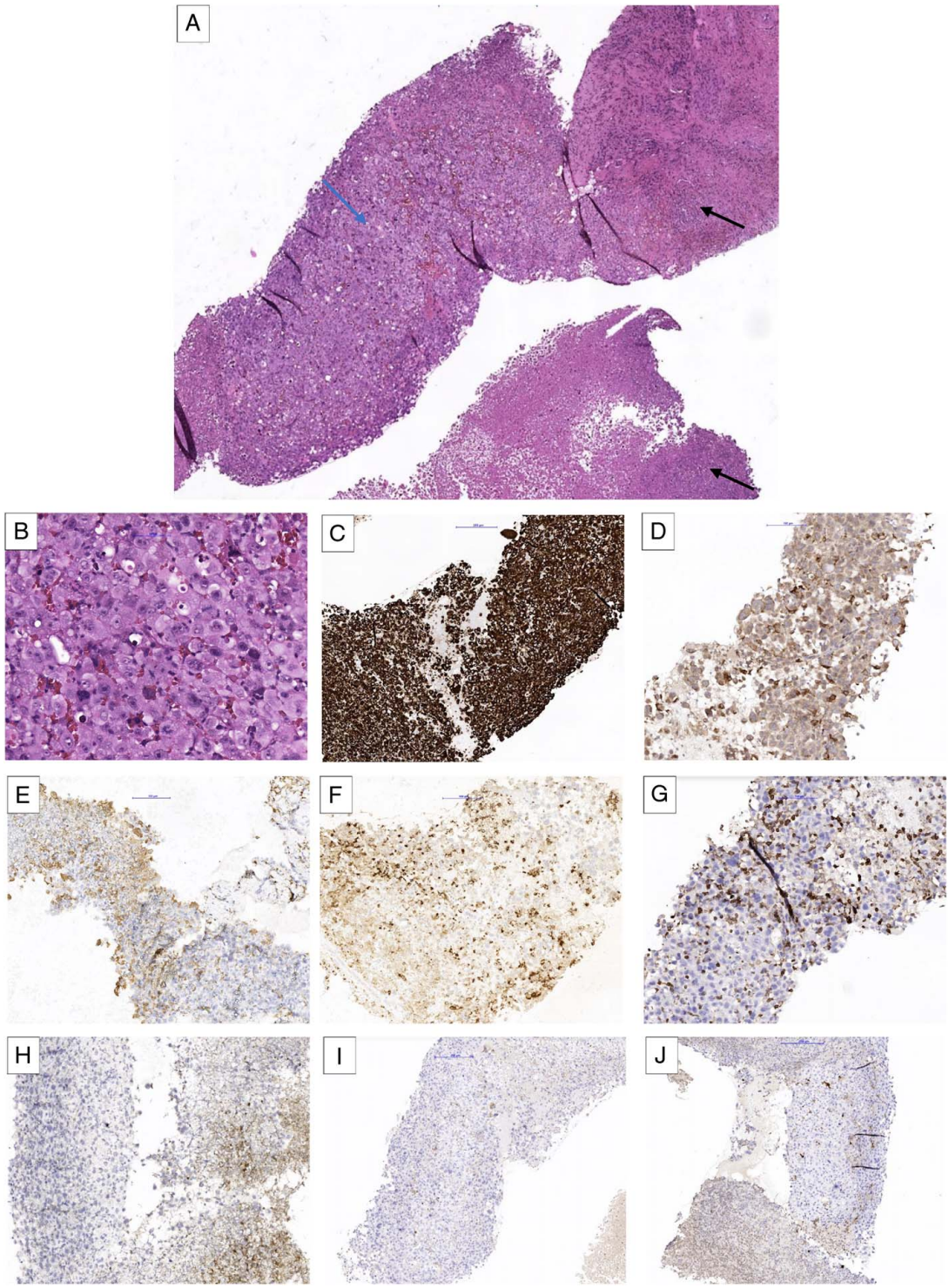

Figure 2. Histopathological and Immunohistochemical images. At low magnification, the biopsy sample revealed a large amount of tumor necrosis (black arrow) while the non-necrosis tumoral cells (blue arrow) are only visible at the middle (A, HE× 50). At high magnification, the tumor was composed of diffuse, large cells showing round or irregular nuclei, vesicle chromatin, prominent nucleoli and abundant, eosinophilic cytoplasm (B, HE× 400). The tumor cells reacted positively with Vimentin (C), CD68 (D), CD163 (E), lysozyme (F) and negatively with LCA (G), MPO (H), CK (I), and S100 (K).

Langerhans cell histiocytosis in this case. Metastatic melanoma was also excluded because of the positivity with histiocytic markers and the negativity with S100. Therefore, our patient had the final diagnosis of HS.

HS usually presents at an advanced stage and has a rapidly progressive clinical course, in which most patients died within 2 years of diagnosis[3]. Moreover, there were no improvements of survival rate of HS during the 15-year period from 2000 to 2014

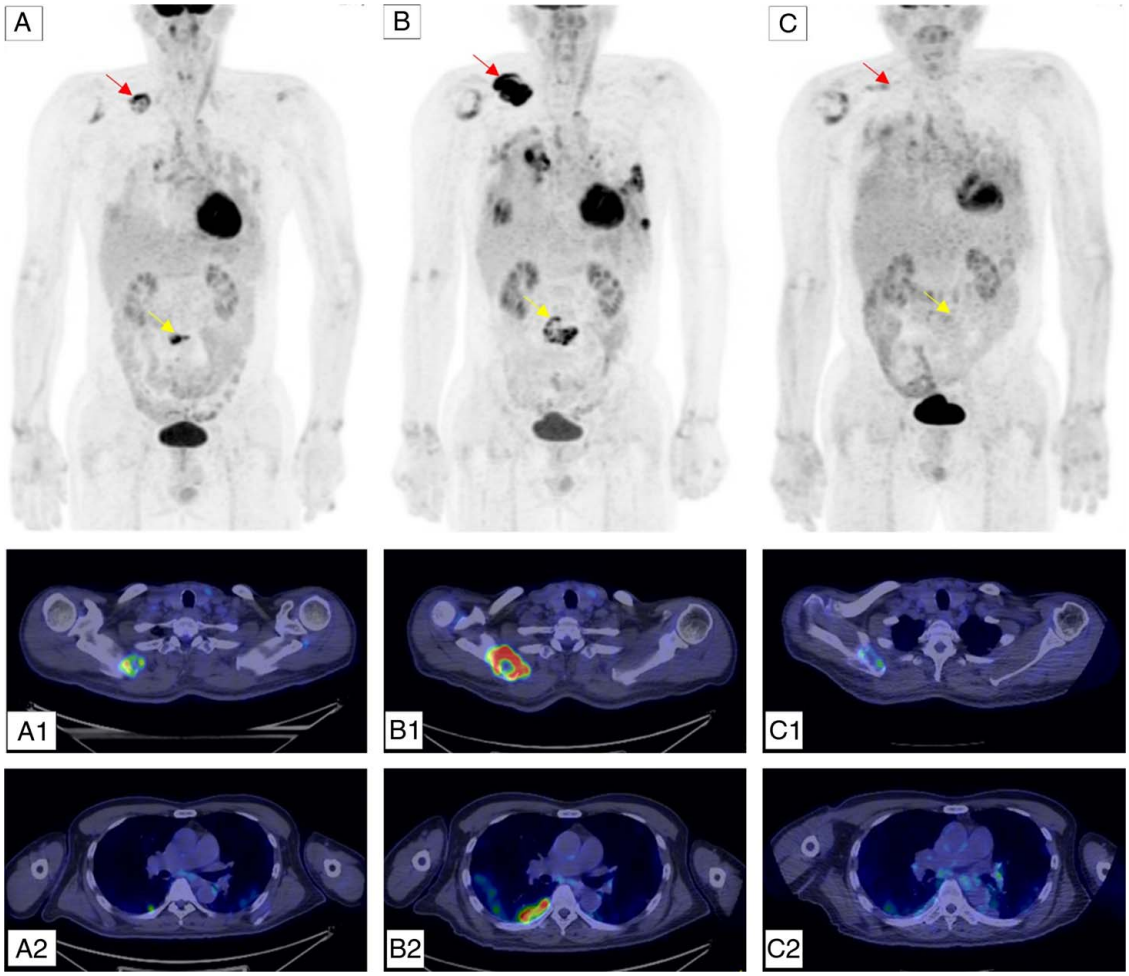

Figure 3. Pretreatment and re-evaluation PET/CT images. (A) Staging PET/CT images showed multiple FDG-avid lesions in right shoulder (red arrow), L4 vertebra (yellow arrow), lung, pleura (A2) and mediastinal lymph nodes. The shoulder tumor had a high FDG metabolism (SUV max of 12.0) (A1). In the postchemotherapy PET/CT, the disease progressed in all sites (B); the primary tumor (B1) and pleural lesions (B2) increased in size and level of FDG-uptake. After three cycles of pembrolizumab, PET/CT (C) illustrated a significant response.

according to the SEER database[1]. The most common therapy for advanced disease was lymphoma-based chemotherapy regimens such as CHOP, etoposide, and alkylating drugs, with limited success[5]. Some novel agents such as thalidomide and alemtuzumab have also been tried in several case reports, showing some initial signs of activity[11,12]. With the advances in molecular and genetic profiling, new potential targets of HS have emerged. Studies using DNA pyrosequencing showed that the BRAF V600E mutation was recorded in about 62% of HS cases, more frequent than other histiocytic and dendritic cell neoplasms[13]. This not only shed new lights on the understanding of the disease but also provide a viable target for therapy. Vemurafenib, a BRAF-inhibitor has been shown to bring good initial response in some individual cases[14,15]. Besides, a recent study showed that 3 out of 12 (25%) patients with HS had strong and diffuse PD-L1 expression[6]. Another study evaluating immunotherapy markers in histiocytic neoplasms also demonstrated that HS might have higher a tumor mutational burden (TMB) compared to other subtypes[16]. These molecular evidence suggests there could be a role of immunotherapy in HS. In our patient, the disease was refractory to chemotherapy and pembrolizumab has been given based on the strong PD-L1 expression. The patient achieved a significant symptom reduction without palliative radiotherapy and has had a progression free survival with over 30 months. Pembrolizumab was tried in another patient in Japan with a response in the primary tumor and bones, but new metastatic lesions also developed[17]. To our best knowledge, our patient is the first case with HS who had a durable response to pembrolizumab. Nivolumab has also been reported to have activity in a patient with HS[18]. However, this patient had a heterogenous response to immunotherapy and pathological evaluation of the resistant site showed loss of PD-L1 expression, which suggested a refractory mechanism to immunotherapy. Immunotherapy also showed efficacy in several cases of other sarcomas of antigen presenting cells such as follicular dendritic cell sarcoma and Langerhans cell sarcoma[19,20]. Interestingly, Zanwar *et al.*[19] suggested that the combination of pembrolizumab and local radiation could be synergistically effective in a patient with malignant histiocytic neoplasm. Therefore, further studies are needed, not only to assess the efficacy of immune checkpoint inhibitors in HS but also to explore the molecular basis of therapeutic effect and resistance to better understand this rare disease.

In our case, tumor mutation burden testing was not done, which is a limitation. TMB has been shown to be a predictive marker of immunotherapy benefit in many solid tumors[21]. However, we did not have this information to put in the context of previous studies and for future evidence synthesis. In the oncology field, there is an increasing effort to utilize immunotherapy to treat a variety of cancers, as well as identifying predictive biomarkers to better select patients for this treatment modality. Our case study has provided initial evidence for further investigations of immunotherapy not only on HS but also other rare tumors with a lack of treatment options.

Conclusions

HS is a rare and aggressive disease with limited treatment options. Immunotherapy might bring sustained disease remission and further studies evaluating the role of immune checkpoint inhibitor in HS are warranted.

Ethical approval

This study was approved by the ethics committee of the Vinmec Times City International General Hospital.

Consent

The patient has given written consent to publish his case (including the publication of photographs).

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Author contribution

L.T.N., G.H.P., P.T.V., and H.G.Y.: all the authors contributed in diagnosis and management the case, performing literature search, writing the paper, and approved the manuscript.

Conflicts of interest disclosures

The authors declare that they have no conflicts of interest.

Research registration unique identifying number (UIN)

This is not a first-in-human study, thus it is not needed.

Guarantor

Assoc. Prof. Hyeon Gyu Yi, MD, PhD.

Data availability statement

Datasets generated during and/or analyzed during the current study are publicly available upon reasonable request.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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