Case Report

A case of adrenal undifferentiated pleomorphic sarcoma with tertiary lymphoid structures responded to pembrolizumab

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Abbreviations & Acronyms
123I-MIBG = 123I-labeled metaiodobenzylguanidine
CIC = colon immune classes
CT = computed tomography
FDG-PET = fluorodeoxyglucose-position emission tomography
MIBG = metaiodobenzylguanidine
MSI = microsatellite instability
PEMBROSARC = pembrolizumab plus cyclophosphamide in soft tissue sarcoma
SIC = sarcoma immune classes
TLS = tertiary lymphoid structures
TMB = tumor mutation burden
UPS = undifferentiated pleomorphic sarcoma

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Introduction: Although undifferentiated pleomorphic sarcomas are aggressive, a subset of these tumors are immunogenic and may respond to immunotherapy.
Case presentation: A 69-year-old man developed bilateral adrenal tumors and underwent bilateral adrenalectomy. Pathological examination revealed undifferentiated pleomorphic sarcoma harboring tertiary lymphoid structures and infiltration of $CD8^+$ T cells. Genome profiling revealed PD-L1 amplification, microsatellite instability, and a high tumor mutation burden. He developed local recurrence and multiple peritoneal dissemination 2 months after surgery; adriamycin chemotherapy was ineffective for these lesions. Sustained complete remission of all lesions was achieved by administering pembrolizumab.
Conclusion: Immunohistochemical analysis focusing on tertiary lymphoid structures and genome profiling to evaluate microsatellite instability and tumor mutation burden are essential for precision medicine and informed clinical decision-making when treating advanced undifferentiated pleomorphic sarcoma.

Key words: immunotherapy, tertiary lymphoid structures, undifferentiated pleomorphic sarcomas.

Keynote message

The presence of tertiary lymphoid structures may be a biomarker for the efficacy of immunotherapy in undifferentiated pleomorphic sarcoma. In patients with tertiary lymphoid structure-positive tumors, genome should be analyzed because pembrolizumab can be used if the tumor mutation burden or microsatellite instability is high.

Introduction

UPS, previously called malignant fibrous histiocytoma, is characterized by no particular differentiation tendency.[1] UPS is one of the most aggressive tumors with a poor prognosis.[2] Among sarcomas, UPS has a relatively high TMB[3] with numerous tumor-infiltrating lymphocytes. Compared with other sarcomas, tumor-infiltrating T cells in UPS present with a greater oligoclonal T-cell receptor repertoire.[4] UPS is therefore considered a highly immunogenic tumor. However, this may be particularly true for only a subset of UPS, due to its heterogeneity. Here, we report a case of UPS in which high immunogenicity was indicated by the presence of TLS in the tumor. Pembrolizumab was administered based on genomic analysis, resulting in sustained complete remission. For advanced UPS harboring TLS, genomic analysis is recommended to consider immunotherapy with pembrolizumab.

Case presentation

A 69-year-old man experienced abdominal discomfort underwent abdominal CT, which revealed weakly enhanced tumors in the bilateral adrenal glands (Fig. 1a). On magnetic resonance imaging, the bilateral adrenal tumors showed signals similar to those of the liver, suggesting bilateral primary adrenal tumors, malignant lymphoma, or metastatic adrenal tumors

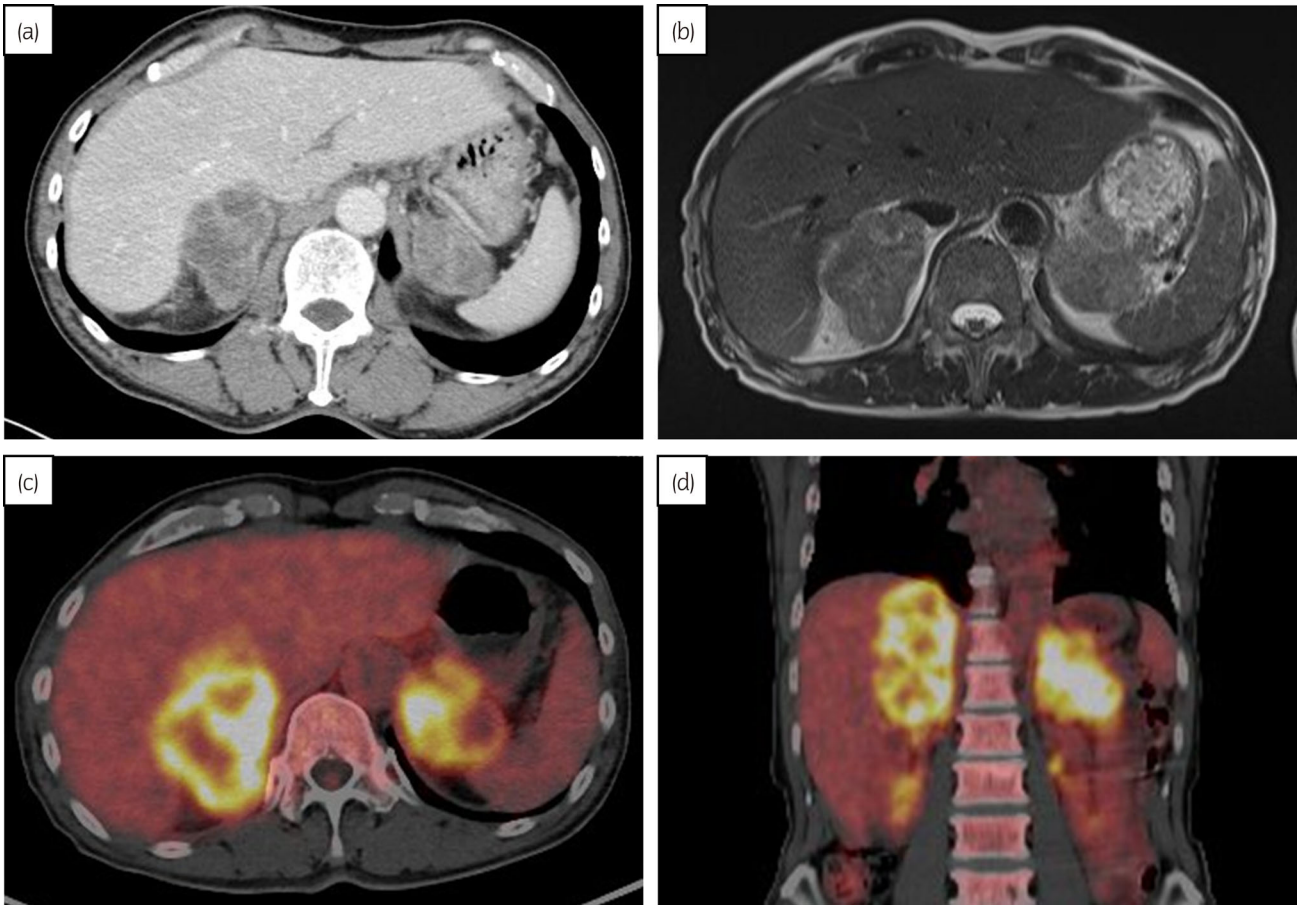

Fig. 1 CT, magnetic resonance imaging, and FDG-PET CT findings of bilateral adrenal tumors. (a) Axial section of contrast-enhanced CT, (b) axial section of T2-weighted magnetic resonance imaging, (c) axial section of FDG-PET CT, and (d) coronal section of FDG-PET CT.

(Fig. 1b). FDG-PET CT showed high FDG uptake in both adrenal tumors (SUV_{max}, 9.34) and direct invasion of the right adrenal tumor to the liver. However, no obvious distant metastasis or other primary cancer was found (Fig. 1c,d). 123I-MIBG scintigraphy revealed no MIBG uptake in the bilateral adrenal tumors. Blood tests showed a mild elevation of soluble IL2 receptor to 938 U/mL (normal, 157–474 U/mL). No other tumor markers were elevated. Endocrinological examinations showed elevation in adrenocorticotropic hormone (134 pg/mL; normal range, 7.2–63.3) and noradrenaline (1745 pg/mL; normal range, 100–450); however, serum levels of cortisol and androgen, and urine levels of normetanephrine and metanephrine were normal.

Considering a preoperative diagnosis of bilateral adrenocortical carcinoma (cT4N0M0), open bilateral adrenalectomy and partial hepatectomy were performed, as the right adrenal tumor had invaded the caudate lobe of the liver. Histologically, the tumors consisted of irregularly proliferated spindle-shaped cells. The tumor cells were positive for vimentin and negative for epithelial membrane antigen; the Ki 67 labeling index was 40%. Desmin, smooth muscle actin, and S100 were all negative, suggesting no specific differentiation. SF-1 was negative; therefore, sarcomatoid change of adrenocortical carcinoma was unlikely. CDK4 and MDM2 were negative; thus, dedifferentiated liposarcoma was ruled out (Fig. 2). Hence, the adrenal tumor was finally diagnosed as UPS. The resection margin was negative for tumor. Clusters of tumor-infiltrating lymphocytes were observed in the tumor margins. These lymphocyte clusters were TLS as they had a central cluster of $CD20^+$ and $CD21^+$ B cells surrounded by $CD3^+$, $CD4^+$, and $CD8^+$ T cells (Fig. 3).

Two months later, FDG-PET CT revealed multiple peritoneal disseminations and local recurrence (Fig. 4a). The patient experienced general malaise and abdominal pain, which rapidly worsened. Despite two courses of systemic chemotherapy with adriamycin, the tumor progressed further. Tumor genetic profiling (FoundationOne CDx) revealed high MSI and TMB, with 16.4 mutations per megabase. Multiple gene mutations were observed (Table S1), including amplification of *CD274* (PD-L1; amplification number 7) and *PDCD1LG2* (PD-L2; amplification number 7).

Immunotherapy with pembrolizumab was initiated because the tumor had TLS with $CD8^+$ T lymphocytes infiltration, and high MSI and TMB. After one course, FDG-PET CT showed reduction in the recurrent tumors (Fig. 4b), and abdominal pain and general malaise improved. After four courses, PET CT showed complete disappearance of both local recurrence and peritoneal dissemination (Fig. 4c). The patient has been receiving pembrolizumab and has remained in complete response for 1.5 years since confirmation of recurrent disease.

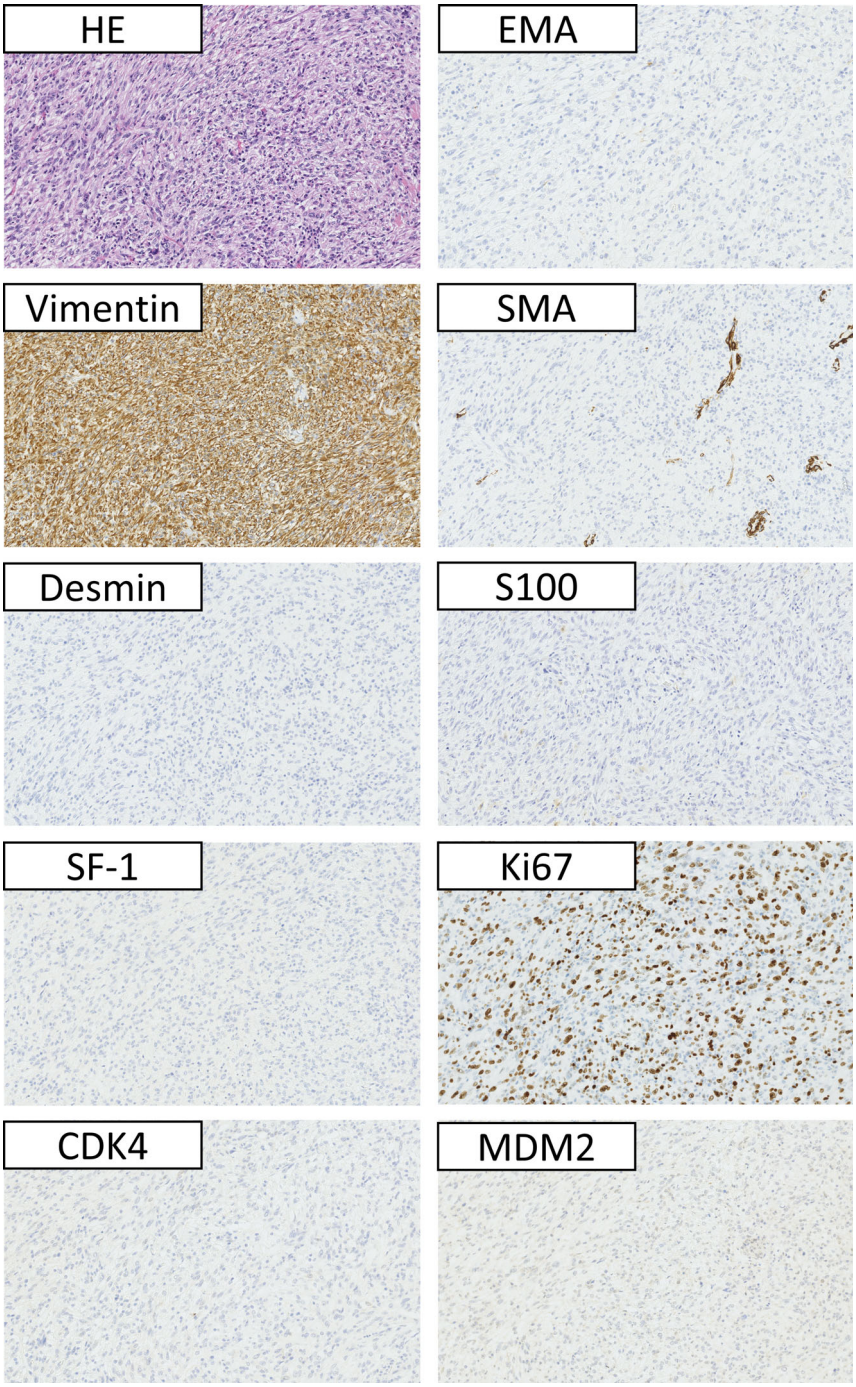

Fig. 2 Immunohistochemical findings of adrenal UPS (all images magnified 200×). Tumors were strongly positive for vimentin. Forty percent of the tumor cells were positive for Ki67, but negative for all other proteins.

Discussion

We present a metastatic UPS case who achieved complete response after receiving pembrolizumab. Immunohistochemical analysis of the primary lesion revealed infiltration of $CD8^+$ T cells and the presence of TLS. Genomic tests also showed PD-L1 amplification, and high MSI and TMB. These findings indicated highly immunogenic tumors that could respond to immunotherapy.

In the SARC028 trial,[5] which investigated the utility of pembrolizumab for soft tissue sarcoma, 7/40 patients responded to pembrolizumab; of these, four had UPS. PD-L1 was expressed in only 2/40 patients (5%); however, both patients had UPS and responded to pembrolizumab. As PD-L1 expression correlates with T-cell infiltration in UPS,[6] PD-L1 expression may predict the efficacy of immune checkpoint inhibitor therapy in UPS.

TLS are ectopic lymphoid tissues that appear in tumors and are responsible for the activation, proliferation, and differentiation of T and B cells. Petitprez *et al*. genetically analyzed soft tissue sarcomas and classified them into five SIC.[7] SIC E (immune and TLS-high) was defined as the tumor that highly expresses a group of genes involved in the activity of $CD8^+$ T cells, natural killer cells, and cytotoxic lymphocytes.

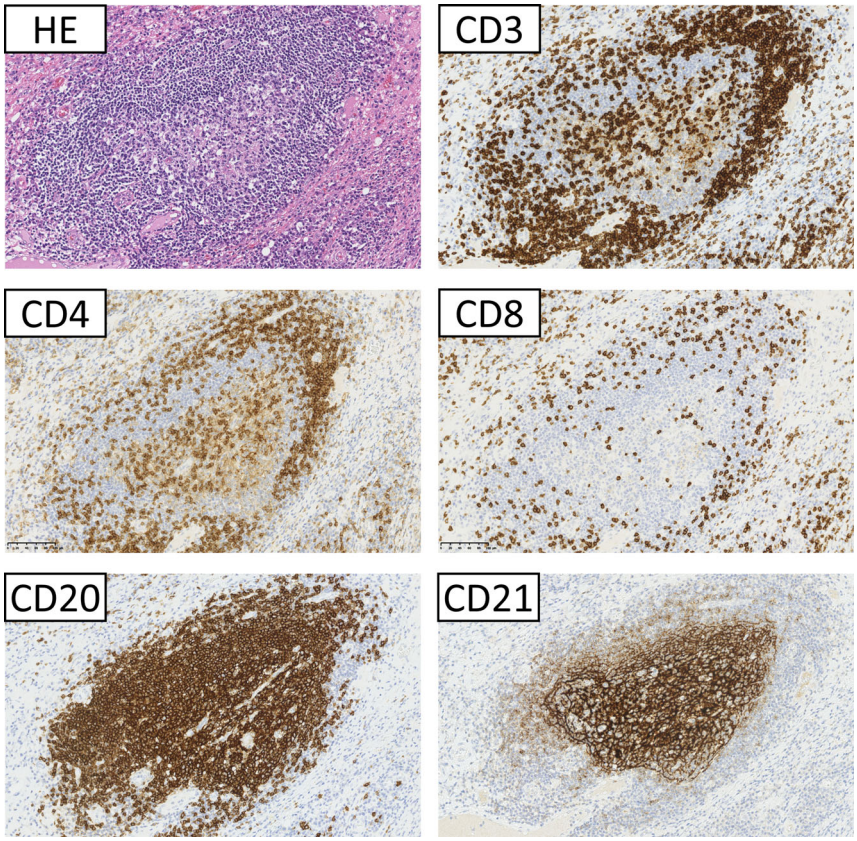

Fig. 3 Immunohistochemical findings of TLS. The accumulation of tumor-infiltrating lymphocytes revealed by hematoxylin and eosin staining were TLS as they had a central cluster of $CD20^+$ and $CD21^+$ B cells surrounded by $CD3^+$, $CD4^+$, and $CD8^+$ T cells.

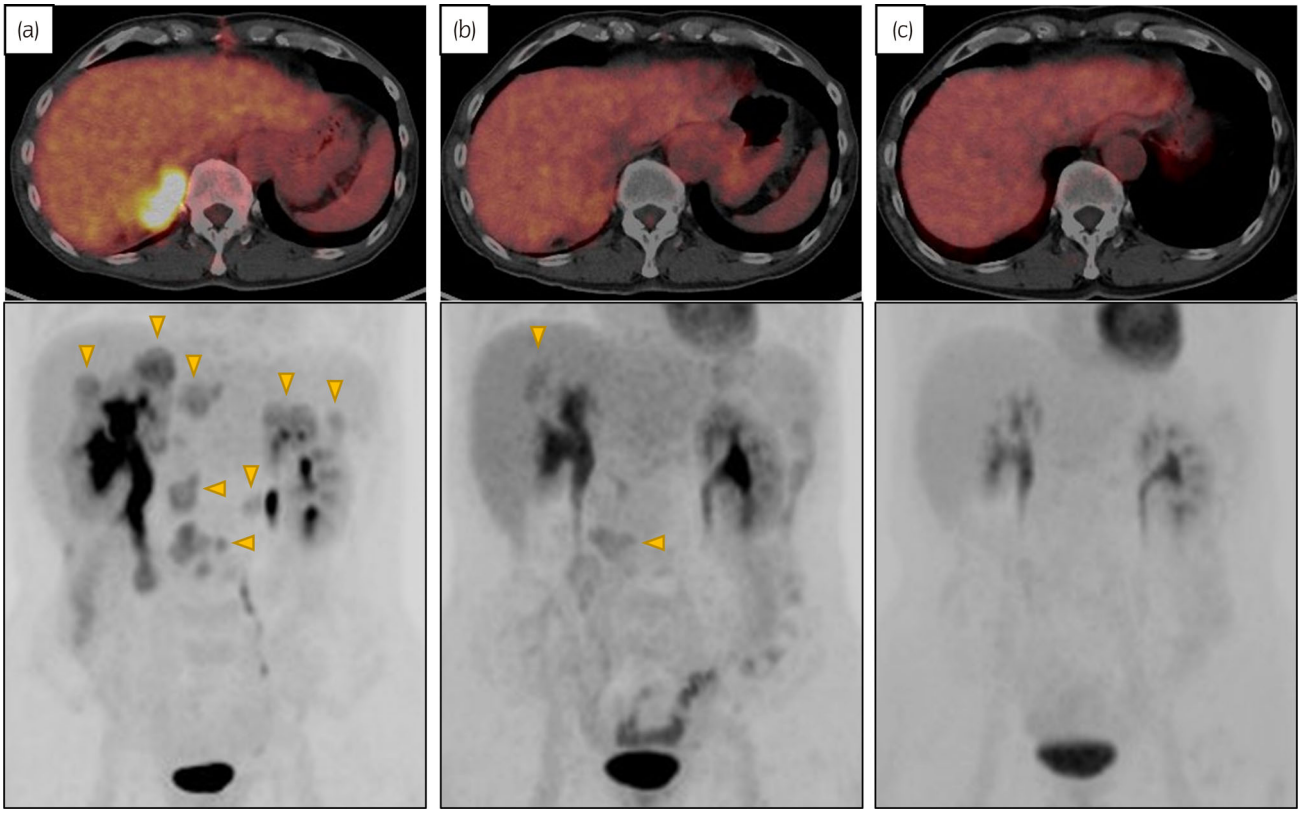

Fig. 4 FDG-PET findings before (a) and after one (b) and four (c) courses of pembrolizumab. In addition to local recurrence on the dorsal side of the liver, numerous peritoneal dissemination lesions were observed before treatment; however, all the lesions regressed after one course, and all disappeared after four courses. Yellow arrowheads indicate peritoneal dissemination lesions.

TLS immunostaining was found almost exclusively in the SIC E group. They reported higher response rates and improved survival with pembrolizumab in the SIC E group in a retrospective analysis of the SARC028 trial, suggesting that TLS may be a biomarker for immunotherapy efficacy in sarcomas. The usefulness of TLS as a biomarker of immunotherapy efficacy was also demonstrated in a clinical study of PEMBROSARC.[8] Of the 240 patients, 48 were TLS-positive and showed a higher response rate (26.7% *vs* 2.1%) and higher progression-free survival than TLS-negative patients (at 6 months, 40% *vs* 4.2%). In other cancers, TLS positivity has been reported to be a predictor of response, independent of PD-L1 positivity and infiltration of $CD8^+$ T cells.[9] Therefore, the evaluation of the tumor microenvironment may be important for precision immunotherapy in patients with sarcoma, and particularly, UPS.

Whether TLS is induced by high TMB and neoantigens has not been elucidated, but reports suggest a possible association between TMB, neoantigens, and TLS. Gunderson *et al.*[10] reported that pancreatic adenocarcinoma tumors with mature TLS harboring germinal centers had significantly more MHC-I-restricted neoantigens than tumors with TLS-negative or early-stage TLS without germinal centers. Xia *et al.*[11] classified colorectal carcinoma tumors into four CIC and reported that $CD20^+$ B cells within TLS were enriched in the CIC D group; notably, most TMB-high tumors were also observed in that group. Therefore, the presence of TLS may indicate tumors with high neoantigen levels and high TMB, and might predict patients responsive to immunotherapy.

In conclusion, pembrolizumab may be effective for UPS, particularly when the tumor has TLS. For TLS-positive cases, genomic analysis should be performed because pembrolizumab is approved for TMB-high or MSI-high tumors.

Acknowledgments

None.

Author contributions

Hidetoshi Kokubun: Writing – original draft. Toshiki Kijima: Conceptualization; writing – original draft; writing – review and editing. Atsuko Takada-Owada: Investigation. Daisuke Mamiya: Data curation. Ryo Kurashina: Data curation. Naoya Okubo: Data curation. Toshitaka Uematsu: Data curation. Kohei Takei: Data curation. Kazuyuki Ishida: Supervision. Takao Kamai: Supervision.

Conflict of interest

The authors declare no conflict of interest.

Approval of the research protocol by an Institutional Reviewer Board

Not applicable.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Registry and the Registration No. of the study/trial

Not applicable.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1