Unexpected Durable Complete Response With Anti–PD-L1 Blockade in Metastatic Undifferentiated Pleomorphic Sarcoma: A Case Report With Host and Tumor Biomarker Analysis

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Background

Soft-tissue sarcomas (STSs) are a heterogeneous group of tumors, representing approximately 1% of adult malignancies.[1] Within STSs, undifferentiated pleomorphic sarcomas (UPSs) are one of the most frequent subgroups (5%-15%).[2] Treatment options of advanced UPS remain limited, and the prognosis of patients with metastatic disease is poor, with a median survival of approximately 12 months.[3] UPS is characterized by a high level of genomic instability, as indicated by its complex karyotype with low tumor mutational burden (TMB) but high copy number alterations.[4,5] This feature can be theoretically associated with higher immunogenicity because of a potential increase in neoantigen formation.[6] For this reason, there is potential role for immunotherapy with immune checkpoint inhibitors (ICIs) in this subset of patients.[7]

Here, we report the case of a patient with metastatic UPS of the chest wall successfully treated with an anti–PD-L1 ICI at the Clinical Trial Unit of the Hospital Clinic of Barcelona (HCB), who experienced an exceptionally prolonged complete response (CR). Because of the lack of biomarkers for the correct identification of patients with UPS benefiting the most from ICIs, an extensive clinicopathological and molecular profiling was performed to explain this uncommon response.

Case Presentation

A 69-year-old man without a relevant medical history was diagnosed in June 2017 at the HCB with a stage IV UPS of the chest wall with one pulmonary metastasis. The patient received standard first-line chemotherapy with doxorubicin + ifosfamide, obtaining stable disease (SD) as best response. A tumorectomy with pulmonary metastasectomy was performed afterward. However, after 2 months, the patient was admitted to our hospital because of seizures. A magnetic resonance imaging (MRI) was performed and showed brain metastasis (Figs 1A and 1B). The lack of previous symptoms and brain imaging prevents to know if it was already present. A new CT scan showed bilateral lung metastases, as well (Fig 1C). The patient was treated with whole brain radiotherapy (WBRT); then, after approximately 1 month, second-line treatment was started with an experimental probody directed against PD-L1. After 8 months of anti–PD-L1 treatment, the patient experienced a CR in extracranial target lesions according to RECIST 1.1 criteria[8] (Fig 1D) and minimal residual changes in brain MRI. After 52 months, the patient discontinued the treatment because of the lack of production of the study drug. In the last reassessment in June 2023, after 71 months, the patient was still with no evidence of disease progression. The clinical case is resumed in Figure 2.

Consent for Publication

The patient provided informed consent to publish the study results on the basis of anonymized data.

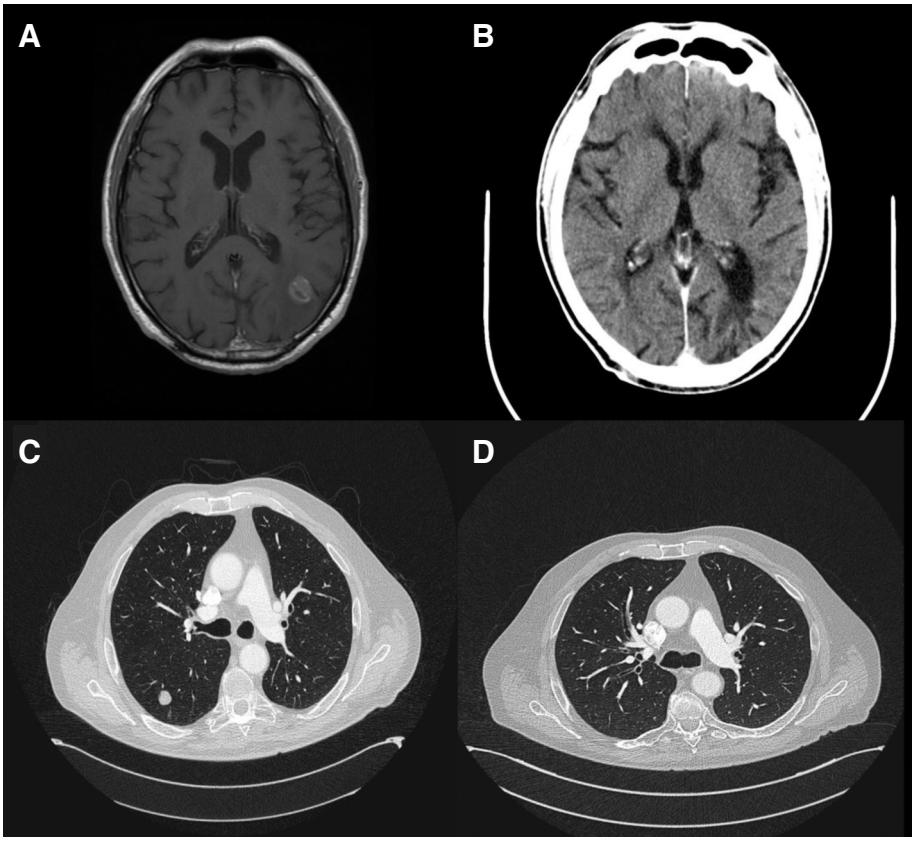

FIG 1. Representative imaging from baseline and at CR in target lesions. (A) CNS metastasis at baseline MRI; (B) CT CNS images at the moment of obtaining a CR (MRI no longer used after baseline); (C) lung metastases at baseline CT scan; the largest lung lesion measured 16 mm in its maximum diameter, with several additional satellite lesions; (D) lung CT scan at the moment of obtaining a CR. CR, complete response; CT, computed tomography; MRI, magnetic resonance imaging.

Molecular Assessments

Host Biomarkers

Previously to start the anti–PD-L1 treatment, we calculated the derived neutrophil-to-lymphocyte ratio (dNLR) and the lung immune prognostic index (LIPI), which we proved to be a highly performing tumor-agnostic prognostic score for ICI-treated patients.[9] The dNLR was 1.51, and the LIPI score was 0, both suggesting a good prognosis.[10,11] Such scores did not substantially change after the first cycle of ICI.

In addition, we performed an exploratory study of the T-cell population in peripheral blood. Blood samples were collected at baseline, at cycle 2, and at each radiologic evaluation. Flow cytometry analyses were performed using the lineage and differentiation markers CD25, CD3, FOXP3, CD40L, HLA-DR, CD4, CD62L, CD69, CD8, CTLA4, CD19, CD16/56, CD28, PDL1, PD1, CD45RO/RA, and CCR7.

Before cycle 1 of anti–PD-L1 treatment, the patient had high blood levels of effector memory T cells with low naïve T cells. At the time of CR, the naïve T cell increased from 9.3% to 21.5% with a decrease of 15% in effector memory T cells. When the patient did not receive the anti–PD-L1 treatment at cycle 10, the naïve T-cell population was 9.9%, similar to baseline (Fig 3A). However, T subpopulations levels in blood did not show a clear pattern in relation to treatment response and maintenance. NK lymphocytes and Tregs showed undulatory noninformative patterns(Fig 3B). At the same time, B-cell levels in blood showed a substantial increase through time (Fig 3C).

Tumor Biomarkers

To interrogate genomic alterations of well-known genes altered in cancer that might both potentially explain the unexpected therapeutic response, as well as representing potential future targets, we performed a molecular testing in pretreatment formalin-fixed paraffin-embedded (FFPE) tumor tissue through the Oncomine Focus assay (ThermoFisher Scientific, Waltham, MA; Table 1). This next-generation sequencing (NGS)–based assay detected the following pathogenetic hotspot mutations: *BRAF* G469V, *FGFR4* W460Ter, *NRAS* G12S, and *PIK3CA* H1047R.

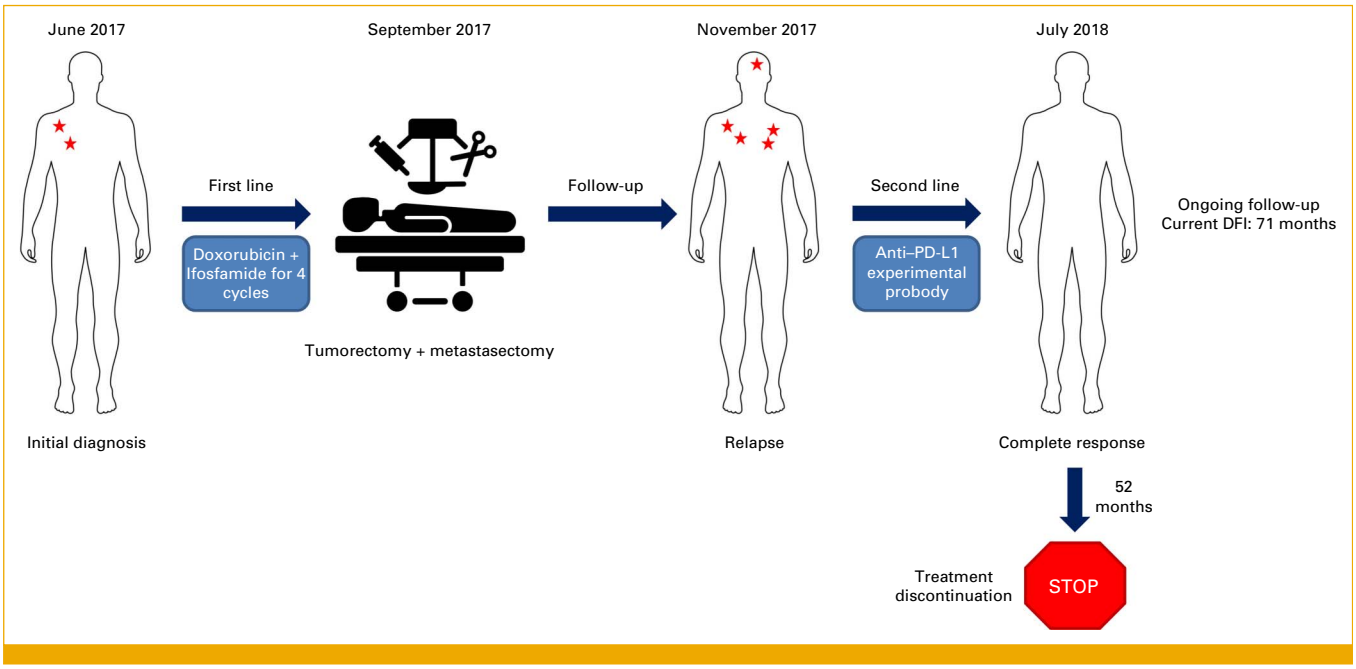

FIG 2. Case report timeline. The first-line scheme consisted in doxorubicin 50 mg/m^2 in continuous infusion at day 1 plus ifosfamide 2,000 mg/m^2 with MESNA uroprotection for 3 consecutive days, administered once every 3 weeks. Whole-brain radiotherapy was administered to reach a total of 30 Gy to stabilize the brain lesion. The experimental probody directed against PD-L1 was administered once every 2 weeks, in cycles of 8 weeks. DFI, disease-free interval.

FFPE tumor tissue was used to perform a gene expression-based assay[12] with a Nanostring nCounter platform (Nanostring Technologies, Seattle, MA) at our laboratory. The assay included cancer- and immune-related genes, including *PDCD1* (PD1) expression, which we considered worthy assessing in this context (Table 2). The PD1 mRNA level detected was -3.657 (relative transcript abundance), meaning high levels of expression according to the cutoff from Paré et al[14] predicting benefit with anti-PD1 ICI. With the same assay, we compared the levels of expression of multiple immune genes associated with B cells, T cells, innate immunity cells, and cytokines, as well as the established immunoglobulin G (IGG) signature, originally identified in breast tumors (Table 2).[13] The mean mRNA levels for IGG-related genes and of all immune genes taken together were higher than mean mRNA levels of all the 192 genes included in the research-based PAM50 codeset (ANOVA P = .029; Fig 3D). The relative transcript abundance of the IGG signature and of all immune genes together corresponded to the 72nd and 58th percentile of the entire codeset, respectively.

PD-L1 was evaluated using immunohistochemistry (IHC) 22C3 pharmDx (Agilent, Santa Clara, CA). PD-L1 was positive with a combined positive score of 70%. We also checked for the presence of high microsatellite instability (MSI-H) at IHC, but no MSI-H was observed at baseline.[15] Additionally, we explored the tumor microenvironment in the primary tumor through IHC and found a high CD4$^+$ and CD8$^+$ T-cell infiltration with low CD20$^+$ (B cells) and FOXP3+ Tregs infiltration (Fig 4). We also assessed in hematoxylin and eosin slides from FFPE samples the presence of tertiary lymphoid structures (TLSs), which are ectopic lymphoid tissues identified as highly organized lymphoid nonencapsulated aggregates resembling secondary lymphoid organs.[16] No TLS were found.

Discussion

UPS is a rare and difficult-to-treat solid tumor with limited therapeutic options.[3] Recently, several phase II studies investigated the outcomes of anti-PD1/PD-L1 ICIs in patients with advanced sarcoma.[3,17,18] Responses were observed only for some histological subtypes, including UPS, with a 40% objective response rate to anti-PD1 in the SARC028 trial.[17] Other studies showed similar results, suggesting that a subset of patients with UPS may respond to immune checkpoint blockade.[19,20] On the basis of this evidence and considering the poor performance of chemotherapy beyond first-line, immunotherapy with ICIs is recommended by the National Comprehensive Cancer Network guidelines for refractory UPS.[21] Nevertheless, the PEMBROSARC phase II trial demonstrated that in an unselected population, the clinical benefit of ICI was extremely limited, with a 6-month nonprogressing rate of 4.9% (95% CI, 0.6 to 16.5) and an overall response rate of 2.4% (95% CI, 0.1 to 12.9).[18] However, results were impressive when intratumor TLSs were observed.[18] These evidences suggest that ICIs can be beneficial to patients with sarcoma, including UPS, but correct biomarker identification is essential.[22] In our case, no TLS was observed at baseline, despite impressive response to ICI. Interestingly, the patient had good prognosis according to

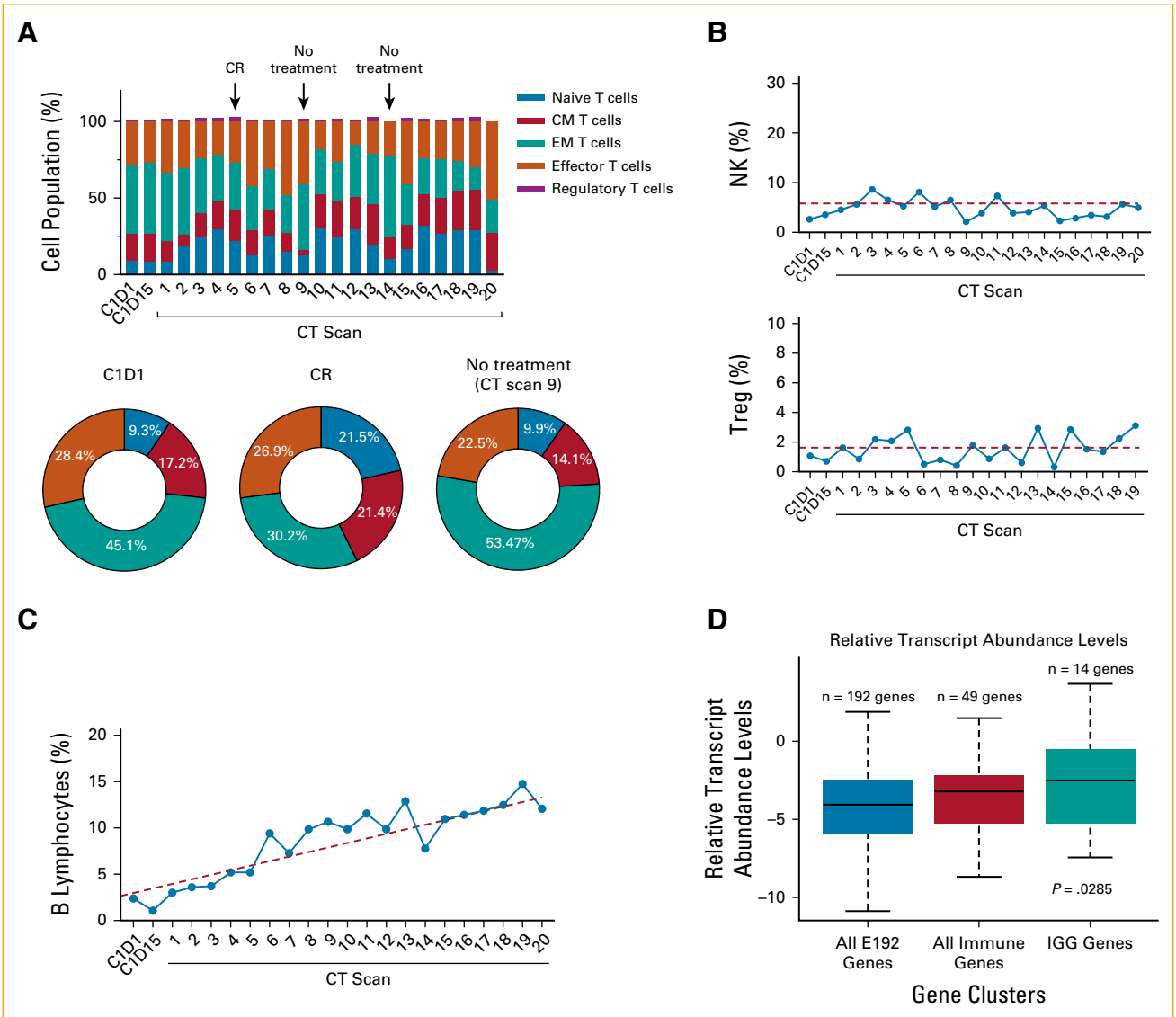

FIG 3. Lymphocyte subpopulations levels at different time points and immune genes relative transcript abundance. (A) Circulating T lymphocyte subpopulations levels at different time points; (B) circulating NK and Tregs lymphocyte subpopulations levels trends through time; (C) circulating B lymphocyte subpopulations levels trends through time; (D) boxplots of mRNA levels of different gene clusters. The numbers 1-20 (A-C) are referred to the number of TAC evaluation. Red lines (B and C) are representative of the different lymphocytes levels trends. C1, first cycle; CM, central memory; CR, complete response; CT, computed tomography; D1, cycle day 1; D15, cycle day 15; EM, effector memory; IGG, immunoglobulin G; NK, natural killer; Tregs, regulatory T lymphocytes.

both basal LIPI score and dNLR, confirming that these scores provide valuable prognostic information in patients with solid tumors treated with immunotherapy.[9,11,23]

It has been reported that UPSs present with a high expression of genes related to both antigen presentation and T-cell–mediated immunity and is among the most mutated STS subtypes, suggesting that it may be well suited to treatment with ICI.[24] Unfortunately, we could not measure the TMB of our patient's tumor, which is an established biomarker of response to ICI with anti-PD1 pembrolizumab.[25] However, not many genomic mutations were found, nor were observed alterations clearly associated with immunotherapy benefit. Conversely, the presence of *BRAF* G469V and *NRAS* G12S mutations suggested a possible hyperactivation of the RAS/MAPK pathway, which usually confers poor prognosis in UPS.[26] An *FGFR4* mutation was observed, as well (ie, *FGFR4* W460Ter), which is a driver gene for rhabdomyosarcomas.[27] Despite these potentially unfavorable mutations, our patients showed an impressive response to ICI with a durable CR that translated into a disease-free interval of almost 6 years, which is uncommon.

Interestingly, our patient received WBRT 1 month before starting anti–PD-L1 treatment. This approach could have increased the permeability of the blood-brain barrier and

TABLE 1. List of Genes Included in the Oncomine Focus Gene Panel

Oncomine Gene Panel					
Hotspot Mutation Target Gene		CNV Target Gene		Pathogenetic Fusions Involved Gene	
AKT1	*IDH1*	*AKT1*	*MYCN*	*ABL1*	*NTRK3*
ALK	*IDH2*	*ALK*	*PDGFRA*	*AKT3*	*PDGFRA*
AR	*JAK1*	*AR*	*PIK3CA*	*ALK*	*PPARG*
BRAF	*JAK2*	*BRAF*	—	*AXL*	*RAF1*
CDK4	*KIT*	*CCND1*	—	*BRAF*	*RET*
CTNNB1	*KRAS*	*CDK4*	—	*EGFR*	*ROS1*
DDR2	*MAP2K1*	*CDK6*	—	*ERBB2*	—
EGFR	*MAP2K2*	*EGFR*	—	*ERG*	—
ERBB2	*MET*	*ERBB2*	—	*ETV1*	—
ERBB3	*MTOR*	*FGFR1*	—	*ETV4*	—
ERBB4	*NRAS*	*FGFR2*	—	*ETV5*	—
ESR1	*PDGFRA*	*FGFR3*	—	*FGFR1*	—
FGFR2	*PIK3CA*	*FGFR4*	—	*FGFR2*	—
FGFR3	*RAF1*	*KIT*	—	*FGFR3*	—
GNA11	*RET*	*KRAS*	—	*MET*	—
GNAQ	*ROS1*	*MET*	—	*NTRK1*	—
HRAS	*SMO*	*MYC*	—	*NTRK2*	—

Abbreviations: CNV, copy number variation.

TABLE 2. List of Genes Included in the Custom 192-Gene Panel

PAM50 E192 Gene Panel					
ABCC11	*CD7*	*EOMES*	*IL18R1*	*MKI67*	*RRM2*
ACTG2	*CD79A*[a]	*ERBB2*	*IL23A*	*MLPH*	*S100A9*
ACTR3B	*CD84*	*ERBB3*	*IL2RG*[a]	*MMP1*	*SERPINB5*
AFF3	*CD86*	*ERBB4*	*IL34*	*MMP11*	*SFRP1*
AGR2	*CD8A*	*ESR1*	*IRF1*	*MND1*	*SH2D1A*
AGR3	*CDC20*	*ETFA*	*IRF4*	*MPHOSPH6*	*SIAH2*
ANLN	*CDC6*	*EXO1*	*IRF8*	*MRAS*	*SLAMF1*
AR	*CDCA1*	*F12*	*ISG20*	*MSLN*	*SLC39A6*
ASPM	*CDCA5*	*FA2H*	*ITK*	*MUCL1*	*SPDEF*
AURKA	*CDCA8*	*FGFR1*	*KCTD9*	*MYBL2*	*STARD3*
BAG1	*CDH3*	*FGFR2*	*KIF23*	*MYC*	*STAT1*
BCL2	*CDKN3*	*FGFR4*	*KIF2C*	*NAT1*	*STAT4*
BIRC5	*CENPA*	*FHOD1*	*KLK5*	*NDRG2*	*TCAP*
BLVRA	*CENPF*	*FOXA1*	*KLRB1*	*NECTIN4*	*TFCP2L1*
BOC	*CEP55*	*FOXC1*	*KLRD1*	*NEK2*	*THSD4*
BRCA1	*CLUAP1*	*GABRP*	*KNTC2*	*NFIB*	*TMEM45B*
BRCA2	*CNTNAP2*	*GAPD*	*KRT14*	*NQO1*	*TNFRSF17*[a]
BUB1	*CREB3L4*	*GARS*	*KRT17*	*NTN3*[a]	*TOP2A*
C2orf54	*CRYAB*	*GATA3*	*KRT18*	*ORC6L*	*TROP2*
CCNB1	*CTLA4*	*GNLY*	*KRT5*	*ORMDL3*	*TRPV6*
CCNB2	*CX3CL1*	*GPNMB*	*KRT6B*	*PDCD1*	*TSPAN13*
CCND1	*CXCL13*	*GPR160*	*KYNU*	*PGR*	*TTK*
CCNE1	*CXCL8*[a]	*GRB7*	*LAX1*[a]	*PHGDH*	*TYMS*
CD19	*CXCL9*	*GSDMB*	*LGALS9*	*PIM2*[a]	*UBE2C*
CD2	*CXCR6*	*GZMA*	*LY9*	*PNMT*	*UBE2T*
CD27[a]	*CXXC5*	*GZMB*	*MAGED2*	*POU2AF1*[a]	*XBP1*
CD274	*DGKD*	*HLA-C*[a]	*MAPT*	*PSMD3*	*ZNF552*
CD3D	*DNAJC12*	*ID4*	*MDM2*	*PTTG1*	*ACTB*
CD3G	*DNALI1*	*IGJ*[a]	*MELK*	*PUM1*	*MRPL19*
CD4	*E2F1*	*IGKC*[a]	*MFSD2A*	*RAD51*	*PSMC4*
CD40	*EAF2*	*IGL*[a]	*MIA*	*RB1*	*RPLP0*
CD68	*EGFR*	*IGLV3-25*[a]	*MID1*	*RRAGA*	*SF3A1*

[a]Identifies the 14 genes integrating the immunoglobulin G signature. These genes are implicated in the maturation of T and B lymphocytes progenitors (*IL2RG*), $CD4^+$ and B lymphocytes activation and survival (*CD27, TNFRSF17, PIM2*), B lymphocytes differentiation in germinal centers (*POU2AF1*), immunoglobulin production (*CD79a, IGJ, IGKC, IGL, IGLV3-25*), chemotaxis (*CXCL8, NTN3*), and regulation of B, T, and NK lymphocytes activity (*LAX1, HLA-C*).[13]

improved the brain metastasis response, as suggested from studies conducted in other tumor types. This combined approach might thus merit further evaluation in wider cohorts also in the context of UPS.[28-30]

Importantly, high PD-L1 protein levels were observed at baseline. This biomarker has been associated with response to ICI directed against the PD1/PD-L1 axis in multiple trials,[31-33] a predictive potential that seems to find confirmation in our case. However, PD-L1 is a suboptimal biomarker since different and not interchangeable assays and methodologies for assessment are available, with different indications depending on the tumor and leading to different ICI prescriptions.[31,34] Moreover, several meta-analyses led to opposite conclusions.[22] Noteworthy, PD1 mRNA levels were also considered high, if taking into account the cutoff for prediction of anti-PD1 ICI benefit recently established in a pan-cancer context.[14,33] This biomarker has the advantage over PD-L1 to be detectable with a standardized and high reproducible methodology and might be applied potentially in all solid tumors. In our case, it successfully predicted anti–PD-L1 benefit. Hence, we believe that further confirmation of its predictive potential should be pursued, also in the context of patients treated with anti–PD-L1 ICI. In this perspective, the ongoing trial SOLTI-1904 ACROPOLI (ClinicalTrials.gov identifier: NCT04802876) will likely provide more solid evidence on this promising biomarker.

Another common biomarker of response to anti-PD1 ICI is the presence of MSI-H, a condition usually associated with DNA mismatch repair deficiency (dMMR).[15] In fact, two prospective trials have demonstrated, so far, that solid malignancies with MSI-H/dMMR experience clinically meaningful response rates with durable effect over time when treated with anti-PD1 pembrolizumab or dostarlimab,[15,35] leading to a tumor histology-agnostic approval by the US Food and Drug Administration for both ICIs. However, in our case, there was no MSI-H at baseline, suggesting other potential mechanisms underlying the response obtained to immunotherapy.

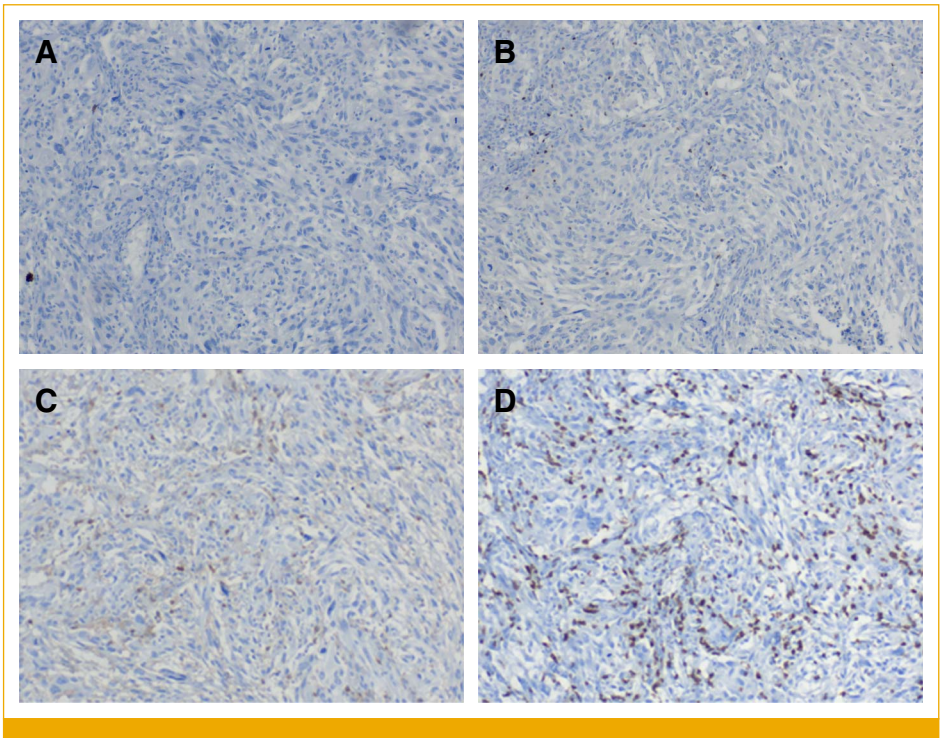

FIG 4. Representative images of immune infiltrate in the patients' tumor. (A) $CD4^+$ T-helper lymphocytes; (B) $CD8^+$ cytotoxic T lymphocytes; (C) $CD20^+$ B lymphocytes; (D) FOXP3+ regulatory T lymphocytes (Tregs). All pathology images are magnified at 40×. +, positive; Tregs, regulatory T lymphocytes.

Interesting from a biologic perspective is the finding that peripheric B lymphocytes levels increased during the treatment and basal levels of the IGG immune signature were higher than overall mean gene expression. This signature seems to reflect adaptive immune response activation mostly associated with B-cell response and immunoglobulin production and was associated with more favorable outcomes in the aggressive triple-negative breast cancer subtype.[36] Interestingly, we recently observed in a publicly available data set from The Cancer Genome Atlas that the IGG signature was associated with better overall survival in STS (hazard ratio, 0.78 [95% CI, 0.62 to 0.97]; $P = .029$).[37] Another study showed that TLSs enriched in B cells in sarcoma's microenvironment are associated with better prognosis and response to immunotherapy,[38] though in our case there were no TLSs in baseline tumor tissue. Overall our case, along with these findings, suggest that anti–PD-L1 ICIs are an effective treatment option in UPS and that B-cell immunity is likely responsible for the antitumoral effect of this therapeutic approach in this disease. Moreover, B cells can contribute to the upregulation of T-cell responses. In our patient's tumor microenvironment, high cytotoxic T-cell infiltration was observed, with reduced Tregs infiltrates, usually negative regulators of antitumoral immune responses,[39] consistent with the recent report from a subcohort of the PEMBROSARC trial.[40] Whether this might be a proxy for tumor immune sensitivity should be further clarified.

Finally, although B-cell infiltrates were not extensive at baseline, circulating B lymphocytes progressively increased throughout the treatment, raising the question of whether B-cell levels might represent a good tool to monitor therapeutic response. Unfortunately, we had no available posterior biopsy to evaluate potential treatment-induced modifications in the tumoral immune infiltrate and correlate B lymphocyte levels through time and TLSs in the tumor microenvironment, which have been elsewhere associated with response to ICIs in sarcoma.[38]

Conclusions

Despite being a poor prognostic disease, metastatic UPS can be successfully treated with immunotherapy interfering with the PD1/PD-L1 axis. The correct selection of optimal candidates for such a therapeutic approach is imperative, considering the high costs and potential life-threatening toxicities associated with immune checkpoint blockade.[41,42] In this perspective, PD-L1 levels or PD1 mRNA at baseline might be useful to identify candidates. In addition, the role of WBRT to increase the therapeutic response to ICIs in UPS with brain metastasis

should be assessed. Considering the prognostic role and the potential association between response to ICI and B-cell immunity, the role of baseline IGG signature merits further exploration to define its role as predictor of response to anti-PD1/PD-L1 inhibitors. Similarly, the role of peripheric B lymphocyte levels as a tool to monitor antitumor response also merits further evaluation in prospective wider cohorts.

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DISCLAIMER

Any views, opinions, findings, conclusions, or recommendations expressed in this material are those solely of the author(s) and do not necessarily reflect those of Funding Entities.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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