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Articles

Immunohistochemical analysis of PD-L1, CD4, CD8, CD20, and PU.1 expression in dedifferentiated chondrosarcoma: the clinical and prognostic value

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Background: Dedifferentiated chondrosarcoma (DDCS) is a rare and extremely aggressive type of mesenchymal bone tumors, with a biphasic structure represented by the classical chondrosarcoma elements, usually of low or intermediate grade, combined with a sharp transition to a highly malignant (high-grade) non-cartilaginous sarcoma. The DDCS is associated with a poor outcome, low effectiveness of medical therapy and high mortality rates. Immunotherapy is emerging as a promising therapeutic approach, necessitating comprehensive characterization of the tumor's immunological profile and its microenvironment.

Objective: To evaluate the expression of inflammatory markers in the tumor stromal infiltrate PD-L1, CD4, CD8, CD20, and PU.1 in primary DDCS specimens. This analysis aims to identify novel prognostic and therapeutic targets, as well as potential predictors for treatment efficacy.

Methods: We retrospectively analyzed immunohistochemical (IHC) data from tumor samples obtained from 42 patients with DDCS (18 males and 24 females aged 24 to 94 years; median age 65 years). The analyzed specimens of DDCS contained two components: well-differentiated chondrosarcoma and poorly-differentiated non-cartilaginous sarcoma represented by pleomorphic undifferentiated sarcoma (n = 33), osteosarcoma (n = 6), rhabdomyosarcoma (n = 2), and angiosarcoma (n = 1). The IHC analysis was performed with a Ventana BenchMark ULTRA automated immunostainer (Ventana Medical Systems, USA) with optimized protocols for anti-PD-L1 antibodies (clone SP142) and manually with staining for anti-PU.1 anti-CD4, anti-CD8, and anti-CD20 antibodies. PD-L1 expression was evaluated separately in the dedifferentiated and chondroid components of the tumor cells. Samples containing PD-L1-expressing lymphocytes were counted separately.

Results: PD-L1 expression in the dedifferentiated tumor component was detected in 40% (17/42) of the cases, in the chondroid component in 26% (11/42), and in both tumor components in 17% (7/42) of the specimens. No association was found between PD-L1 expression in various tumor components and clinical or morphological disease characteristics. The median survival was 68.6 months in PD-L1-negative patients compared to 7.7 months in PD-L1-positive ones ($p = 0.096$). The mean cellular composition in the dedifferentiated tumor component consisted of 17.3 ± 12.8% macrophages, 4 ± 3.5% $CD4^+$ T cells, 4 ± 2.4% $CD8^+$ T cells, and 6.7 ± 3.8% B cells. The analysis of immune cell infiltration patterns demonstrated that higher B-cell infiltration of the tumor was typical for earlier disease stages ($p = 0.045$). No prognostic significance was established for the stromal markers studied; however, high macrophage infiltration of the DDCS samples showed a trend toward unfavorable disease course ($p = 0.112$). The number of $PU.1^+$ cells in the tumor stroma positively correlated with PD-L1 expression in both chondroid ($r = 0.357$, $p = 0.028$) and dedifferentiated ($r = 0.343$, $p = 0.033$) tumor components, as well as with T-cell counts ($r = 0.402$, $p = 0.014$).

Conclusion: The results of the IHC analysis of PD-L1, CD4, CD8, CD20, and PU.1 expression indicate the clinical and prognostic significance of the immune microenvironment of DDCS, suggesting new possibilities for the disease prognosing and development of immune therapies. Nevertheless, further studies in larger patient cohorts are needed to more precisely determine the clinical significance of these identified markers.

Key words: dedifferentiated chondrosarcoma, PD-L1, CD4, CD8, CD20, PU.1, expression, prognosis, immune therapy

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Dedifferentiated chondrosarcoma (DDCS) is a rare example of highly aggressive variant of mesenchymal bone tumors with well-documented morphological, radiological, and clinical characteristics. This tumor type comprises 1–2% to 10% of all chondrosarcomas and commonly affects patients over 50 years of age, distinguishing it from osteosarcoma, which primarily occurs in adolescents and young adults under 30 years [1, 2]. The defining characteristic of this tumor variant is its biphasic structure, consisting of conventional chondrosarcoma components, typically of low- to intermediate-grade, with an abrupt transition to high-grade non-cartilaginous sarcoma [3]. While conventional chondrosarcoma exhibits relatively indolent growth and limited responsiveness to chemo- and radiotherapy, the dedifferentiated type, on the contrary, demonstrates rapid progression and high metastatic potential. Although systemic therapy is frequently employed for DDCS, unlike its conventional counterpart, the disease prognosis remains extremely poor [4].

The DDCS develops from a low-grade chondrosarcoma through the accumulation of genetic and epigenetic alterations that disrupt the cellular differentiation and proliferation control, including in *IDH1, IDH2*, and *TP53* mutations, *CDKN2A* inactivation, and aberrant expression of MDM2 and CDK4. These molecular abnormalities make the DDCS resistant to many conventional treatments and account for the tumor's aggressive clinical course [1, 5, 6]. Despite advances in molecular oncology, targeted therapies for this tumor type remain elusive. The immune microenvironment of DDCS is characterized by profound immunosuppression, chronic inflammation, and attenuated antitumor immune responses [7]. The key features include the predominance of tumor-associated macrophages, primarily of the M2 phenotype, which promote immune suppression and extracellular matrix remodeling. These macrophages secrete immunosuppressive mediators, including interleukin-1 receptor antagonist, interleukin-10, and transforming growth factor-β, creating conditions that compromise the cytotoxic capacity of $CD8^+$ T lymphocytes against tumor cells [8].

Regulatory T cells (Tregs) also play a crucial role in immunosuppression by inhibiting the activity of natural killer (NK cells) and $CD8^+$ T cells. High Treg infiltration is associated with poor prognosis in numerous solid tumors, as these cells contribute to tumor immune resistance, whereas elevated $CD8^+$ T cell infiltration is associated with favorable outcomes [9, 10]. Furthermore, tumor cells frequently express PD-L1, enabling immune evasion through T cell suppression and inhibition of proliferation and activity [11]. These factors collectively create an immunosuppressive environment in which DDCS demonstrates minimal response to immune checkpoint inhibitor therapy (anti-PD-1, anti-CTLA-4), resulting in insufficient antitumor immune responses to counter the disease progression. Isolated reports suggest that certain immunotherapeutic approaches including pro-inflammatory cytokines, oncolytic vaccines, and adoptive T cell transfer have shown efficacy in bone and soft tissue sarcomas, but not in DDCS [12, 13]. Therefore, this study aimed to analyze the expression of PD-L1, CD4, CD8, CD20, and PU.1 markers in inflammatory stromal infiltrates within the primary DDCS specimens to identify novel prognostic and therapeutic targets, as well as potential predictive biomarkers of treatment efficacy.

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Methods

We retrospectively analyzed primary tumor specimens from 42 patients with DDCS (18 males and 24 females, aged 24 to 94 years; median age 65 years) who were diagnosed and treated at the N.N. Blokhin National Medical Research Center of Oncology from 2012 to 2023. The study protocol had been approved by the Ethics Committee of the N.N. Blokhin National Medical Research Center of Oncology (date of the protocol 02.09.2021). Clinical data, including age, sex, histological subtype of the dedifferentiated component, disease stage, and tumor differentiation grade, were extracted from medical records of the patients. Inclusion criteria comprised the histologically confirmed diagnosis, availability of archival tissue specimens, and complete clinical data. Exclusion criteria consisted of incomplete follow-up data, prior neoadjuvant chemotherapy, and concurrent malignancies.

Immunohistochemical (IHC) analysis was performed with both an automated Ventana BenchMark ULTRA IHC staining system (Ventana Medical Systems, USA) and with manual staining for anti-PU.1, anti-CD4, anti-CD8, and anti-CD20 antibodies. The automated protocol utilized anti-PD-L1 antibody (clone SP142, Ventana Medical Systems, USA), while manual staining was conducted with antibodies against PU.1 (clone 9G7, Cell Signaling Technology, USA), CD4, CD8 (clone C8/144B, Dako, USA), and CD20 (clone RM272, Sigma-Aldrich, USA). Target cells were identified with universal

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detection system OptiView DAB Universal IHC Detection Kit (Ventana Medical Systems, USA) according to manufacturer's specifications. In-house positive tissue controls (tonsil, placenta, and non-small cell lung cancer specimens) were used for the protocol validation for PD-L1 IHC staining.

Immunostaining was evaluated by an Olympus BX53F microscope (Olympus, Japan) to quantify the percentage of positive cells in each population studied. PD-L1 expression was evaluated independently in both the dedifferentiated and chondroid tumor components. Special attention was given to specimens containing PD-L1-positive lymphocytes. The samples were categorized into two groups based on the PD-L1 expression status (positive or negative).

Statistical analyses were performed with GraphPad Prism 10.0 software. The D'Agostino test was employed to assess normality of distribution before selecting appropriate statistical methods for the assessment of the significance of the differences. Student's t-test was used for the groups comparisons, and associations between variables were evaluated with Pearson's correlation coefficient. Contingency tables were analyzed with Fisher's exact test and chi-square test. For survival analyses, the patients were stratified according to the tumor cell PD-L1 status (positive or negative) or median percentage of the microenvironmental immune cells. Survival curves were generated using the Kaplan-Meier method. The follow-up duration was calculated from the date of surgery to either patient's death or his/hers last clinical contact. The differences were tested for significance with the log-rank test. Statistical significance for group comparisons and correlations was defined as $p < 0.05$.

Results

Microscopic examination showed that the dedifferentiated tumor consisted of 2 components: a highly differentiated chondrosarcoma and a low differentiated non-cartilaginous sarcoma. Pleomorphic undifferentiated sarcoma was diagnosed most frequently (33 cases), osteosarcoma in 6 cases, rhabdomyosarcoma in 2 cases, and angiosarcoma in 1 observation. The description of clinical and morphologic characteristics is given in Table 1.

The analysis of PD-L1 expression in the DDCS specimens demonstrated the following patterns. PD-L1 expression in the dedifferentiated tumor component was found in 40% (17/42) of the cases, in the chondroid component in 26% (11/42), and in both tumor components in 17% (7/42). An example of the IHC staining for PD-L1 is given in Fig. 1.

The analysis of clinical significance of PD-L1 expression showed that none of the evaluated clinical and pathological parameters studied (age, sex, histological tumor subtype, differentiation grade, disease stage, and presence of dedifferentiated components at diagnosis) was associated with PD-L1 expression in either the dedifferentiated component, chondroid component, or both components of DDCS (Table 2).

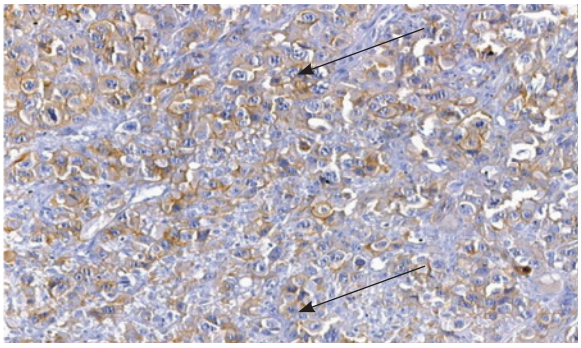

Fig. 1. PD-L1 immunohistochemistry. Positive PD-L1 expression in the nuclei and cytoplasm of the tumor cells and tumor-infiltrating lymphocytes in a polymorphous cell sarcoma sample of dedifferentiated chondrosarcoma (arrows). Micro specimen (×200)

PD-L1 expression in neoplastic cells, particularly in the dedifferentiated component of the tumor, demonstrated a trend toward unfavorable outcome (hazard ratio 3.150; $p = 0.096$) (Table 3).

The median survival duration of the patients with PD-L1-negative DDCS was 68.6 months, compared to 7.7 months for the patients with PD-L1-positive tumors (Fig. 2).

Table 1: Characteristics of patients with dedifferentiated chondrosarcoma

Parameter	Number of cases
Sex:	
Male	18
Female	24
Tumor differentiation grade:	
G1	22
G1–2	15
G3	5
Stage:	
II	21
III–IV	21
The dedifferentiated component at diagnosis:	
Identified	16
Not identified	26

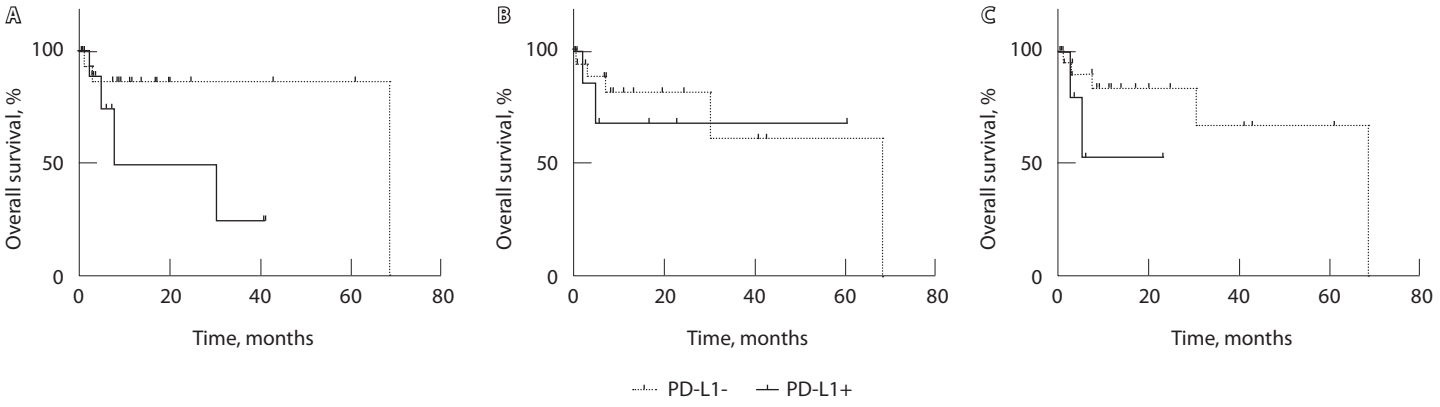

Fig. 2. Prognostic significance analysis of PD-L1 expression in various components of the dedifferentiated chondrosarcoma: overall survival of the patients depending on their PD-L1 expression in dedifferentiated (**A**), chondroid (**B**), and both (**C**) components of the tumor. PD-L1-, no PD-L1 expression; PD-L1+, PD-L1 expression present

Table 2: The association of PD-L1 expression with clinical and morphological features of dedifferentiated chondrosarcoma

Characteristics, N	The dedifferentiated tumor component			The chondroid tumor component			Both components present in the sample		
	PD-L1+	PD-L1-	p	PD-L1+	PD-L1-	p	PD-L1+	PD-L1-	p
Age:									
< 65 years	6	17	0.058	5	18	0.504	2	21	0.214
> 65 years	11	8		6	13		5	14	
Sex:									
Male	7	11	> 0.999	5	13	> 0.999	3	15	> 0.999
Female	10	14		6	18		4	20	
Histological type:									
Undifferentiated sarcoma	13	20	0.639	8	25	0.409	5	28	0.603
Osteosarcoma	2	4		3	3		2	4	
Rhabdomyosarcoma	1	1		0	2		0	2	
Angiosarcoma	1	0		0	1		0	1	
Tumor differentiation grade:									
G1	9	13	0.574	5	17	0.729	5	17	0.427
G1–2	7	8		4	11		2	13	
G3	1	4		2	3		0	5	
Stage:									
II	7	14	0.530	5	16	> 0.999	2	19	0.409
III–IV	10	11		6	15		5	16	
Dedifferentiated component at diagnosis:									
Yes	6	10	> 0.999	7	9	0.070	3	13	> 0.999
No	11	15		4	22		4	22	

N, number of cases; PD-L1+, expression of PD-L1 present; PD-L1-, expression of PD-L1 absent

We also performed the IHC analysis of the inflammatory infiltrate phenotype in the dedifferentiated component of the tumors. The pan-macrophage marker PU.1 was utilized to identify macrophages within the tumor stroma, while CD4 and CD8 markers were used to identify T lymphocytes, and CD20 to identify B lymphocytes (Fig. 3).

Macrophages constituted the predominant immune cell population within the DDCS microenvironment. Mean macrophagal content in the dedifferentiated tumor component comprised 17.3 ± 12.8%, while $CD4^+$ T cells, $CD8^+$ T cells, and B cells represented 4 ± 3.5%, 4 ± 2.4%, and 6.7 ± 3.8% respectively.

There was a significant association between $CD20^+$ cell counts in the tumor and the disease stage, namely, a higher B-cell infiltration being characteristic of earlier disease stages (p = 0.045). Additionally, tumors with dedifferentiated components identified at initial diagnosis demonstrated significantly higher infiltration with both macrophages (p = 0.003) and B-cells (p = 0.017) (Table 4). While none of the studied markers showed any significance as an independent prognostic factor (Fig. 4), it is noteworthy that high macrophagal infiltration of DDCS demonstrated a trend towards an unfavorable disease course and outcome, with median survival times being two-fold different between the high and low infiltration groups (30.5 months versus 68.6 months, hazard ratio 3.205; p = 0.112).

The correlation analysis between PD-L1 expression and immune cell infiltration in the tumor stroma demonstrated that the $PU.1^+$ cells counts in the stroma exhibited significant positive correlations with PD-L1 expression both in chondroid and dedifferentiated tumor components (r = 0.357, p = 0.028; r = 0.343, p = 0.033, respectively), as well as with T cell counts (r = 0.402, p = 0.014).

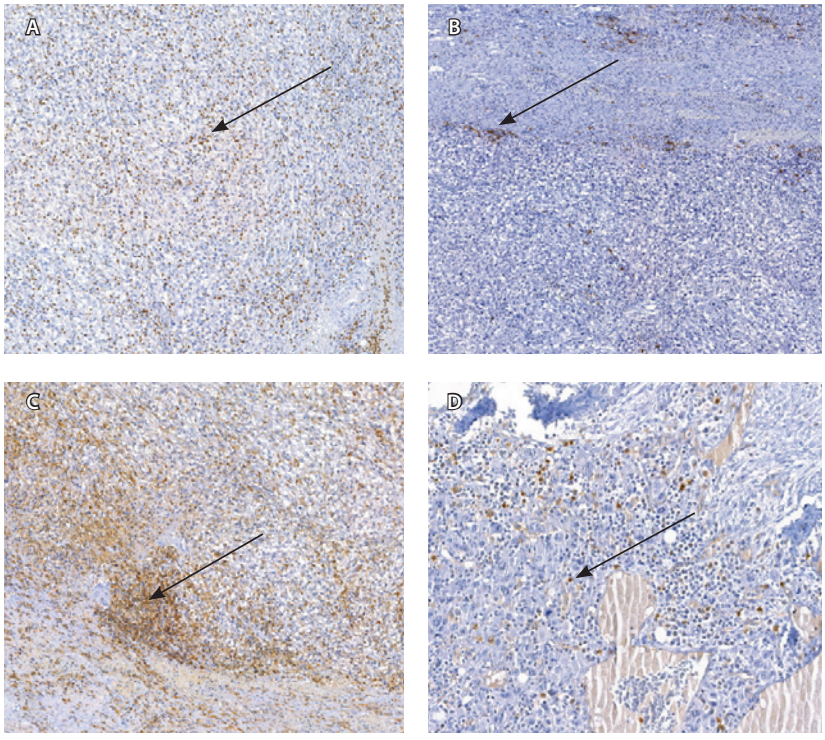

Fig. 3. Immunohistochemical images. Expression of PU.1 (**A**), CD20 (**B**), CD4 (**C**), and CD8 (**D**) markers in the tumor-infiltrating lymphocytes in the samples of dedifferentiated chondrosarcoma (arrows). Micro specimen (×100)

Discussion

This study investigated the tumor microenvironment of DDCS, a rare mesenchymal neoplasm characterized by poor prognosis and limited therapeutic options. With active implementation of immunotherapy into solid tumor treatment, there is particular interest in analyzing the cell composition of the immune infiltrate, as it significantly influences therapeutic efficacy [14]. We have identified PD-L1 expression in 40% of the dedifferentiated

Table 3: The statistical analysis of the prognostic significance of PD-L1 in dedifferentiated chondrosarcoma

High / low PD-L1 expression	Univariate analysis		
	HR	95% CI	p
Dedifferentiated component	3.150	0.6230–15.93	0.096
Chondroid component	1.503	0.2440–9.262	0.6143
Both components in the sample	3.122	0.3023–32.25	0.1365

CI, confidence interval; HR, hazard ratio

Table 4: The association of the PU.1$^+$, CD4$^+$, CD8$^+$ and CD20$^+$ immune cell counts with clinical and morphological features of dedifferentiated chondrosarcoma

Parameter	PU.1		CD4		CD8		CD20	
	M ± SD, %	p	M ± SD, %	p	M ± SD, %	p	M ± SD, %	p
Age:								
< 65 years	16.8 ± 12.2	0.790	3.7 ± 3.7	0.642	4.4 ± 2.7	0.451	6.6 ± 4.3	0.764
> 65 years	17.9 ± 1 3.9		4.3 ± 3.3		3.7 ± 2.1		7.0 ± 3.4	
Sex:								
Male	21.1 ± 11.2	0.086	5.3 ± 3.2	0.059	4.1 ± 2.2	0.991	7.6 ± 4.1	0.274
Female	14.1 ± 13.5		3.1 ± 3.5		4.1 ± 2.7		6.1 ± 3.5	
Histological type of dedifferentiated component:								
Undifferentiated sarcoma	18.9 ± 13.2	0.411	4.1 ± 3.4	0.893	3.87 ± 2.2		6.8 ± 4.0	0.643
Osteosarcoma	11.0 ± 8.9		3.0 ± 4.4		3.75 ± 2.5		7.5 ± 2.8	
Rhabdomyosarcoma	5*		5.0 ± 7.1		10*		7.5 ± 3.5	
Angiosarcoma	10*		5*		–		2*	
Tumor differentiation grade:								
G1	15.0 ± 12.7	0.451	3.7 ± 3.4	0.740	3.3 ± 2.1	0.110	6.5 ± 4.2	0.877
G1–2	20.7 ± 13.1		4.2 ± 3.8		5.3 ± 2.4		7.3 ± 3.7	
G3	18.0 ± 13.0		5.0 ± 3.5		3.3 ± 2.8		6.6 ± 2.8	
Stage:								
II	18.4 ± 12.1	0.603	4.9 ± 3.4	0.138	3.7 ± 2.7	0.443	8.0 ± 4.2	0.045
III–IV	16.2 ± 13.6		3.2 ± 3.6		4.4 ± 2.1		5.3 ± 2.7	
Dedifferentiated component at diagnosis:								
Yes	24.6 ± 9.9	0.003	5.3 ± 3.4	0.069	4.1 ± 2.2	0.852	9.0 ± 4.4	0.017
No	12.7 ± 12.4		3.2 ± 3.5		4.0 ± 2.6		5.7 ± 3.1	

The values are given as mean percentage of cells and standard deviation (M ± SD, %)

* Absolute numbers

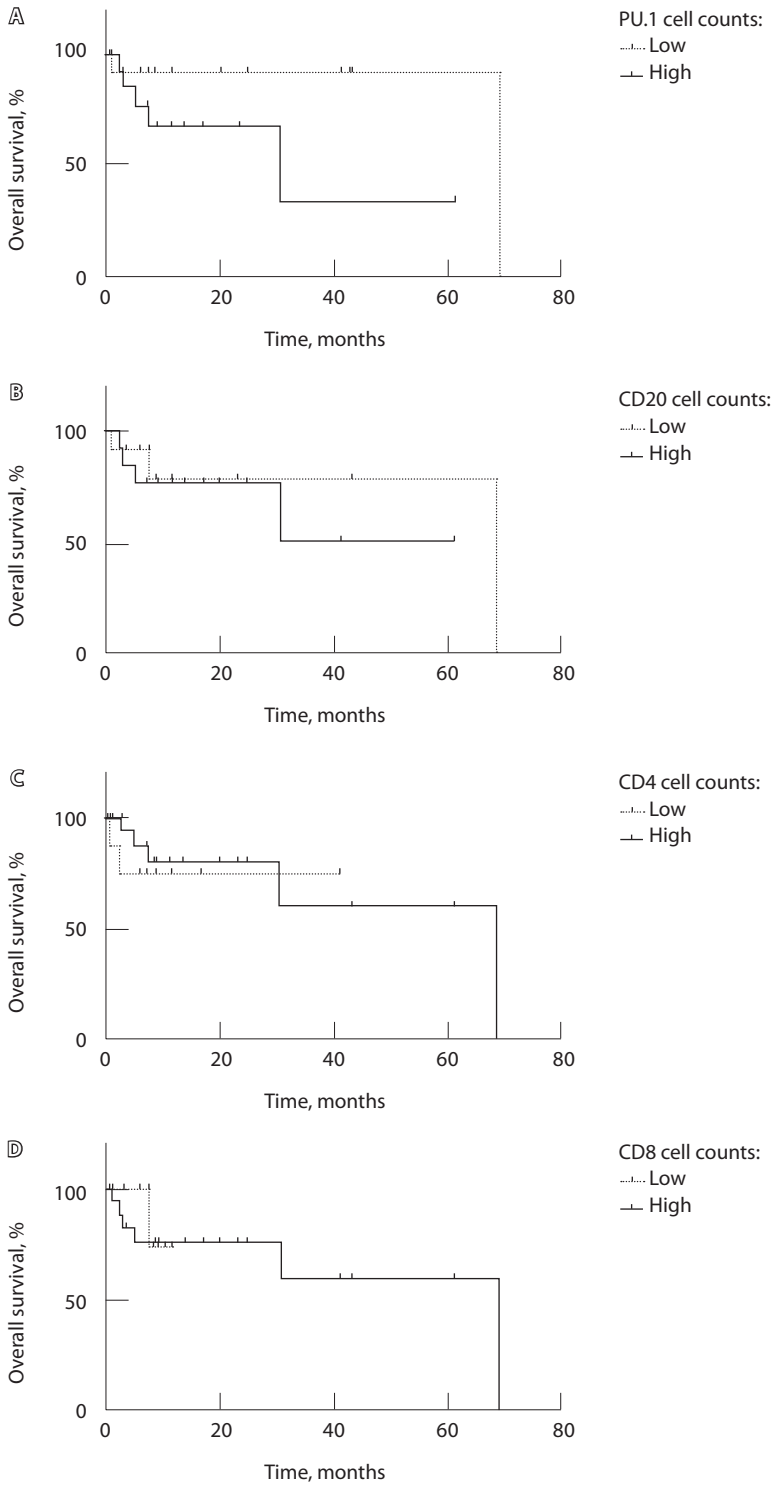

Fig. 4. Overall survival of patients with dedifferentiated chondrosarcoma depending on macrophage (**A**, PU.1$^+$ cells), B lymphocyte (**B**, CD20$^+$ cells), and T lymphocyte (**C**, CD4; **D**, CD8) counts in the stroma of dedifferentiated tumor components. The groups for comparison of survival were formed based on the counts of the microenvironmental immune cells above or below the average

components and in 26% of the chondroid components, which is consistent with previous literature. Thus, M. Kostine et al. reported on PD-L1 expression in 52% of DDCS specimens, which correlated with T cell infiltration of the tumor [7]. Similarly, R. Iseulys et al. analyzed 49 cases of DDCS and detected PD-L1 expression in 43% of the tumor cells [10].

We have found no significant association between PD-L1 expression in various components of DDCS and the basic clinical and morphological characteristics of the disease. The assessment of PD-L1's prognostic significance demonstrated that its expression in the cells within the dedifferentiated component was associated with the trend to an unfavorable disease prognosis. These findings align with results reported by Y. Zhang et al., who found that PD-L1 expression in chondrosarcoma tumor cells correlated with unfavorable outcomes [11]. However, similar studies by R. Iseulys et al. suggest that PD-L1 expression in tumor cells may not consistently be a reliable predictor of the disease course [10].

R. Iseulys et al. hypothesized that PD-L1 expression in stromal cells of the DDCS might function as a favorable prognostic marker. Their study identified three specimens exhibiting PD-L1 expression in stromal lymphocytes, with all patients with these tumor characteristics were alive at the time of analysis. However, this hypothesis requires validation in larger cohorts due to the limited sample size [10]. In general, there is a paucity of research on the clinical significance of immune cell populations in the DDCS development [15]. Our findings corroborate previous reports indicating that macrophages constitute the predominant immune cell population within the tumor stroma [10]. The highest macrophage numbers were found in the dedifferentiated components classified as a undifferentiated sarcoma. Notably, extensive macrophage infiltration of the DDCS demonstrated the trend to an unfavorable disease course, a pattern consistent with observations in most solid tumors [16]. Our study revealed positive correlations between macrophage density in the tumor stroma and PD-L1 expression in both chondroid and dedifferentiated components, as well as T cell infiltration, suggesting potential tumor immunogenicity and their possible responsiveness to immune checkpoint inhibition.

The limitations of this study include its small sample size, retrospective design, and incomplete data regarding subsequent therapeutic interventions and their efficacy.

Conclusion

Our study demonstrated that PD-L1 expression in tumor cells of the DDCS, particularly within the dedifferentiated component, is associated with a poor prognosis and reduced overall survival. Analysis of the immune microenvironment revealed varying densities of macrophages, T and B lymphocytes, with extensive macrophage infiltration potentially indicating more aggressive tumor behavior. The correlation between $PU.1^+$ cell numbers, PD-L1 expression, and T cell infiltration suggests complex interactions between the tumor and the host immune system. These findings highlight the prognostic significance of both PD-L1 expression and macrophagal infiltration in DDCS progression and the need for further investigation of their roles in disease prognosis and treatment.

Additional information

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Conflicts of interests

The authors declare no conflict of interests regarding the publication of this article.

Authors' contribution

N.E. Kushlinskii, the research consept, approval of the final manuscript version; O.V. Kovaleva and A.N. Gratchev, data analysis, text writing; I.V. Boulytcheva and D.V. Rogozhin, clinical data collection, histological studies, text editing; P.L. Prishchep, analysis of the patients' medical files and literature data. All the authors have read and approved the final version of the manuscript before submission, agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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