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Programmed cell death ligand-1 (*PD-L1*) expression in desmoid tumors: a retrospective study

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Abstract. – OBJECTIVE: Desmoid tumor is a rare benign but locally aggressive monoclonal and fibroblastic proliferation. It lacks metastatic potential but is associated with a high local recurrence after surgery. It is either characterized by the Beta-catenin gene (*CTNNB1*) or the adenomatous polyposis coli gene (*APC*) mutation. The most appropriate treatment approach is watchful waiting with periodic follow-ups for asymptomatic patients. However, symptomatic patients who are not good candidates for surgery due to high morbidity risk may benefit from medical therapy. The new drugs targeting programmed cell death protein 1 (*PD-1*) and programmed death-ligand 1 *(PD-L1*) display promising results in many cancer types. This study assessed the *PD-L1* status of desmoid tumors in 18 patients.

PATIENTS AND METHODS: Biopsy and resection materials of 18 patients diagnosed with desmoid tumors between April 2016 and April 2021 were retrieved and assessed for *PD-L1* expression. The prepared slides were immunohistochemically stained with *PD-L1* antibody using Leica Bond® automated immunohistochemistry stainer.

RESULTS: No positive *PD-L1* staining of the desmoid tumor cells was detected in any specimens. Intratumoral lymphocytes were present in all specimens. However, five of them were positively stained for *PD-L1*.

CONCLUSIONS: Based on the results of our study, anti-*PD-1/PD-L1* therapy may not be a valuable option in desmoid tumor treatment due to the lack of expression of PD-L1 by desmoid tumor cells. Nevertheless, the presence of positively stained intratumoral lymphocytes may warrant further studies.

Key Words:
Desmoid tumors, Immunotherapy, *PD-1/PD-L1* expression, Intratumoral lymphocytes.

Introduction

The World Health Organization (WHO)[1,2] has classified desmoid tumors as a clonal fibroblastic proliferation that arises in the deep soft tissues and is characterized by infiltrative growth and a tendency towards high local recurrence but no potential to metastasize (i.e., a benign aggressive lesion). Although they have no metastatic potential, they may cause loss of extremity in case of neurovascular compression and even mortality, especially in intraabdominal lesions[3]. Studies regarding desmoid tumor treatment are ongoing. In recent years, there has been a tendency to proceed with watchful waiting instead of surgery in asymptomatic patients; however, in the case of progressive disease, there is no universally accepted effective medical or surgical treatment yet[4]. Medical treatment, including non-steroidal anti-inflammatory drugs (*NSAIDs*) with or without antiestrogen drugs, low-dose chemotherapy, or tyrosine kinase inhibitors, may be used with variable success and side effects[4-6].

As new cellular pathways are being found and studied, new molecules are being developed, and their efficacy is being studied in various cancer types. Programmed cell death protein 1 (*PD-1*) and programmed cell death ligand-1 (*PD-L1*) were discovered in 1992 and were shown[7] to have an essential role in cancer immune surveillance. The balance of positive and negative signals is as important as the activation of cytotoxic T lymphocytes to develop anti-tumor immunity. Negative signals are usually generated by surface molecules such as cytotoxic T-lymphocyte antigen-4 (*CTLA-4*) and *PD-1*. *PD-1* is an inhibitory

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receptor part of the *CD28* family and is essential in tumor immune escape. *Anti-PD-L1* treatment is recently being investigated in various cancer types[7-13].

PD-L1 is the ligand for *PD-1* and is presented in T cells, B cells, macrophages, and dendritic cells. Activation of the *PD-1/PD-L1* complex reduces antigen-specific T cell activity and decreases the number of antigen-specific T cells by inducing apoptosis. Many studies[14,15] show increased expression of *PD-L1* ligands in various cancers originating from the lung, skin, ovary, cervix, esophagus, breast, bladder, brain, bone, kidney, and liver.

As programmed cell death ligand-1 (*PD-L1*) status has not been thoroughly looked for in desmoid tumors, we aimed to investigate the *PD-L1* status of desmoid tumors to assess possible therapeutic usage of *PD-L1* blockage.

Patients and Methods

Patients diagnosed with desmoid-type fibromatosis had biopsy or resection at the Orthopedics Oncology Unit of the Istanbul Medeniyet University Training and Research Hospital, Goztepe, Istanbul, between April 2016 and April 2021 were included in this study. They had regular follow-ups every six months. Patients who were operated at the General Surgery Department under 18 did not have regular follow-ups. Patients with the diagnosis of familial adenomatous polyposis were not included in the study.

A retrospective study was performed after obtaining ethical approval from Istanbul Medeniyet University Institutional Review Board (approval date: 25.08.2021, number: 2021/0437). Clinico-pathological characteristics such as age and gender and follow-up data (recurrence and outcome) were retrospectively collected from the patient's medical records. Due to the low number of cases, no statistics were performed.

Tissue samples obtained from operation specimens were used to prepare formalin-fixed paraffin-embedded (FFPE) blocks. Sections of 3-micron thickness were taken from these blocks for immunohistochemical analysis. Slides were stained for *PD-L1* antibody (Cell Signaling, E1L3N) using Leica Bond® Automated immunohistochemistry Stainer (Wetzlar, Germany). Placenta and tonsil tissue were used as external control, and intratumoral lymphocytes accompanying some tumors were used as the internal control. Immunoreactivity for *PD-L1* expression was evaluated in the tumor cell membrane and tumor-infiltrating lymphocytes by two of the authors (ANY, TZ) who had no knowledge of the patient's clinical status. Tumor positivity for *PD-L1* was defined as ≥1% tumor cell membrane staining.

Results

There were 25 patients with histologically proven desmoid tumors. We excluded seven patients, including two under 18 years old, three patients who did not have regular follow-ups, two patients who had previous medical treatment elsewhere with tamoxifen, and one with familial adenomatous polyposis. The remaining eighteen patients were included in the study. No positive *PD-L1* staining of the desmoid tumoral cells was detected in any of the specimens. Intratumoral lymphocytes were present in all specimens, and five were positively stained for *PD-L1* (Figure 1-4).

Discussion

Desmoid tumor is a monoclonal and fibroblastic proliferation, however, characterized often by an unpredictable clinical course. It usually occurs between the ages of 15 and 60, with a peak age of around 30. These lesions may be detected at any site of the body but are usually found in the extremities, trunk, and abdomen[16,17].

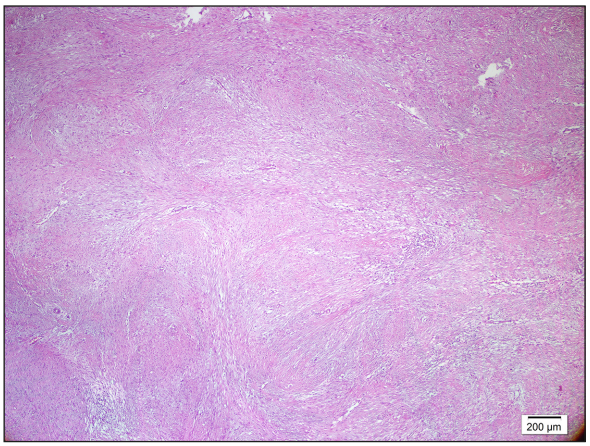

Figure 1. Proliferation of bland spindle cells with no cellular atypia (H&E ×4).

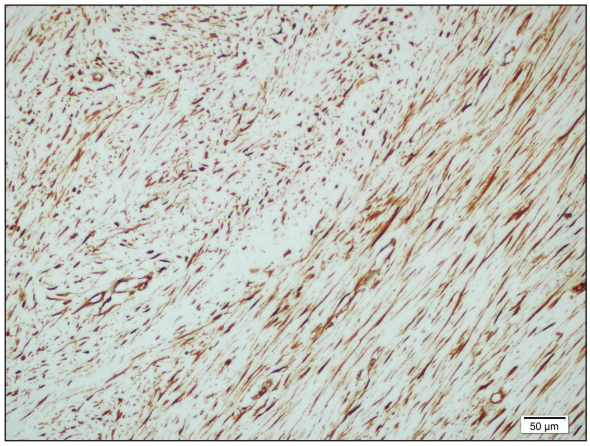

Figure 2. Positive staining with Beta Catenin.

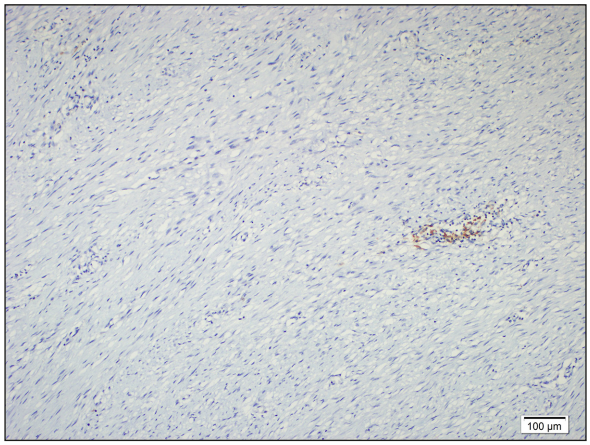

Figure 3. ×10 Negative PDL1 staining of tumoral cells but positive intratumoral lymphocytes.

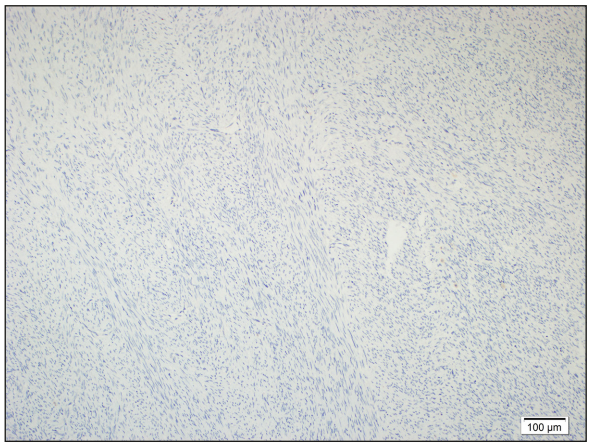

Figure 4. Negative PDL1 staining of tumoral cells.

Although they do not have metastatic potential, they are locally aggressive, with a high recurrence rate after surgical resection. The tumor may grow, proliferate, and progression may occur[17-19].

Nearly 90% of patients have a mutation in the Beta-catenin gene (*CTNNB1*) or the adenomatosis polyposis gene (*APC*). However, different factors are associated with desmoid tumors' development, like estrogen hormone and antecedent trauma. A higher incidence of desmoid tumors is detected during and after pregnancy or oral contraceptive usage, and tumor regression usually occurs during menopause[20-22].

Before commencing treatment, an expert soft tissue pathologist should confirm the diagnosis of the desmoid tumor after the biopsy as they may mimic nodular fasciitis, keloids and solitary fibrous tumor, inflammatory myofibroblastic tumor, low-grade myofibroblastic sarcoma and low-grade fibromyxoid sarcoma[23-27]. Nuclear staining for Beta-catenin aids considerably in diagnosing desmoids; however, confirmation of the diagnosis may be achieved by confirming Beta-catenin gene mutations in selected cases[28,29].

A keloid is a type of scar that results in an overgrowth of tissue at the site of a healed skin injury. It is mostly found on earlobes, sternum, shoulders, upper back, and any place where abrasion has occurred. Histologically it has a very hypocellular stroma with a non-infiltrative growth pattern. Patients have a history of trauma or surgical procedure at the site. Nodular fasciitis is a benign lesion most commonly found in the superficial fascia. It is most common in young people on the upper extremities and trunk. It shows nodular architecture with areas of more loosely arranged, stellate, and tissue culture-like cells. Mitotic activity is more common. Immunohistochemically, Beta-catenin is negative, and it shows a *USP6* gene rearrangement. The solitary fibrous tumor has a classic hemangiopericytoma vasculature with a ropey collagenous background. Immunohistochemically, beta-catenin may be positive, but it is typically diffusely positive for *CD34* and *STAT6*. Inflammatory myofibroblastic tumor is a histologically distinctive myofibroblastic spindle cell neoplasm of borderline malignancy, classically featuring an intermixture of plasma cells and lymphocytes. The most common extrapulmonary sites are the mesentery and omentum, and also occur in the lung and gastrointestinal tract. 50% of all cases have *ALK1* gene rearrangements, and immunohistochemically, beta-catenin is negative. Low-grade myofibroblastic sarcoma is a very

infiltrative lesion with at least focal atypia. It is mainly localized in the head and neck. Immunohistochemically, *SMA* (smooth muscle actin) is positive, and beta-catenin is usually negative. Low-grade fibromyxoid sarcoma is localized primarily in the trunk and deep extremities. It can be rarely localized in the retroperitoneum and mediastinum.

Fibroblastic sarcoma may have positive staining with beta-catenin, but histopathologically, it has more cellular atypia and spindle cells with a herringbone pattern. Low-grade fibromyxoid sarcoma may also be beta-catenin positive. However, it has characteristic curvilinear blood vessels, and there is a *FUS-CREB342* fusion gene which may be detected with fluorescence *in situ* hybridization analyses[30,31].

There are various medical treatment options for patients with advanced diseases. However, these usually are limited to case series or small patient cohorts rather than in a well-controlled clinical setting. Medical therapies usually involve NSAIDS, antihormonal treatment, and traditional cytotoxic chemotherapies. Moreover, in recent years there is also a great interest in targeted therapies[32-34].

Although some case reports or series[35] display the positive effects of antiestrogen treatment alone or in combination with NSAIDs, there is no randomized study with concrete evidence. However, more recently publications[36] found no clear relationship between size, MRI signal changes, and symptomatic relief with tamoxifen treatment.

In case of progression and sustained symptoms after antihormonal and NSAID drug treatment, chemotherapy may be considered[37]. Conventional chemotherapy using low-dose regimens, including methotrexate and vinblastine, or conventional-dose chemotherapy based on anthracycline regimes may be utilized. Pegylated liposomal doxorubicin has also been reported[38,39] to have significant clinical activity with less toxicity than conventional doxorubicin.

New molecules are on the market, and investigations are still going on to find the best effective molecule with minor side effects in progressive cases. Imatinib, a tyrosine kinase inhibitor, achieves stabilization of advanced desmoid tumors but with a low objective response rate[40].

Nilotinib, another tyrosine kinase inhibitor, may be used after imatinib failure to stabilize the lesion's growth. Sorafenib may also be used. However, recent data[15,34,37] about its effectiveness are in the same range as imatinib with no superiority.

In a study[41] conducted with pazopanib, partial responses were reported in three and disease stabilization in five patients.

Due to high morbidity and recurrence risk, there has been a shift from surgery to watchful waiting for asymptomatic patients with desmoid tumors. However, desmoid tumors abutting neurovascular structures and location on mesentery or head and neck region may pose life-threatening complications. Thus, treatment is needed in these cases, and none of the above medical treatments have any definitive beneficial effect on the disease process.

Programmed death ligand 1 is encoded by the *PDCDL1* gene and is found on chromosome 9. It is also known as *B7-H1* or *CD274* and is the first functionally characterized ligand of the co-inhibitory *PD-L1*[42].

In recent studies, *PD-L1* found on tumor cells has an important role in disseminating many tumors. Expression of *PD-L1* has been accepted as a poor prognostic indicator for many different tumors[43]. This pathway is an inhibitor of the immune response, thus the activity of tumor-infiltrating lymphocytes. Equilibrium shifts in favor of tumor cells as the *PD-1/PD-L1* pathway is activated, leading to tumor progression and immunity-induced apoptosis. There is an excellent range of expression rate of *PD-L1* from 19 to 92% in malignant bone tumors. Studies[44-48] show that the expression of *PD-L1* ligand is increased in various cancers originating from the lung, skin, ovary, cervix, esophagus, breast, bladder, brain, bone, kidney, and liver. In the literature[44-48], *PD-L1* expression in tumor cells in 50% of sarcoma cases, including leiomyosarcoma, dedifferentiated liposarcoma, undifferentiated pleomorphic sarcoma (UPS), osteosarcoma, epithelioid sarcoma, and other sarcomas.

According to one[49] of the few studies examining the relationship between desmoid tumors and *PD-L1*, *PD-L1* was negative in all tumor cells in concordance with our study results[49,50]. On the other hand, according to this study, *PD-1* was partially expressed in lymphocytes in the periphery of the tumor. It has been shown that there is no *PD-L1*-driven immune suppression in tumor cells in desmoid tumors. Our study determined *PD-L1* staining intratumoral lymphocytes in 5 of the 20 specimens.

However, Kelany et al[51] found positive *PD-L1* expression in 2/3 of patients in contrast to our study. As dictated by Johnson et al[52], the bidirectional signaling effect of *PD-L1* expressed by

tumor-infiltrating T cells inhibits a network of immune cells needed to create an effective antitumor immune response. *PD-L1* expressed by T cells may be a new target for *PD-L1* blockade therapy, especially for cancers with few tumor cells expressing *PD-L1*. Our study is the first to display the *PD-L1* expression of tumor-infiltrating cells in desmoid tumors.

Limitations

There has been no immunohistochemical staining of *PD-L1* within our patient cohort with desmoid tumors. Although a new generation of drugs targeting *PD-1/PD-L1* displays promising results in especially recent studies[49-52], it may not be a valuable therapeutic option, according to our results, in desmoid tumor treatment. However, positively stained intratumoral lymphocytes may warrant further studies before a definitive decision is reached. The study findings must be confirmed on a larger scale, involving more patients.

Conclusions

This demonstrated a lack of PD-L1 expression in desmoid tumor cells. Intratumoral lymphocytes were positively stained, and this needs further investigation. In desmoid tumors, immunotherapy could be a therapeutic option.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval

This study was approved by the Istanbul Medeniyet University Institutional Review Board (approval date: 25.08.2021, number: 2021/0437).

Informed Consent

Not required due to the retrospective nature of the study.

Authors' Contribution

Ayse Nur Toksoz Yildirim, Muhlik Akyurek, Erhan Okay, Tulay Zenginkinet, Yusuf Iyetin, Korhan Ozkan: contributed to study conception, design, collection of data, data interpretation, preparing the draft manuscript, and final approval of the version to be published.

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Availability of Data and Materials

Data is available to the corresponding author upon request.

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