DOES IMMUNOTHERAPY HAVE A ROLE IN THE TREATMENT OF ENDOMETRIOSIS?

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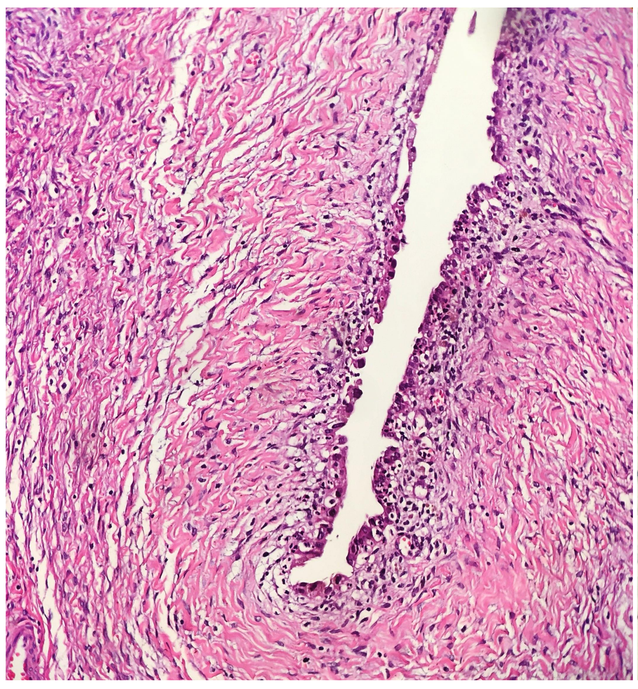
Introduction and Objectives

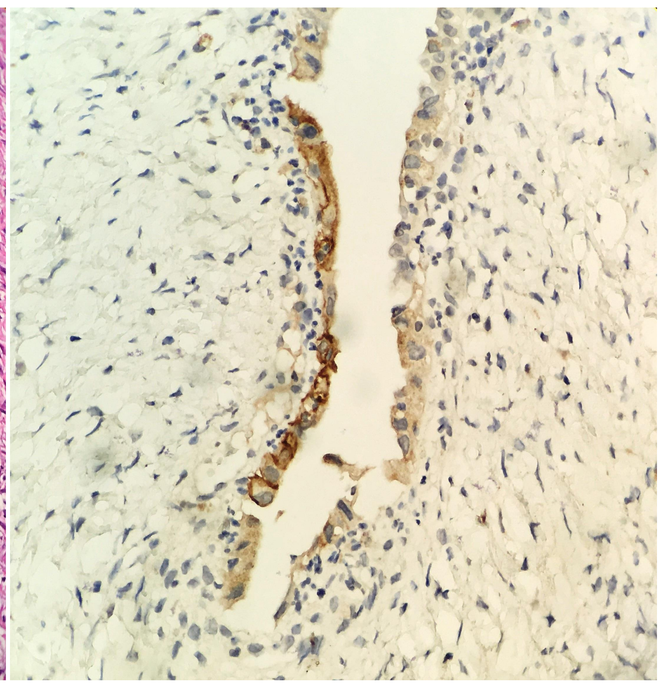
Endometriosis is defined as the presence of endometrial glands and stroma outside the uterine cavity. This estrogen-dependent disorder occurs in approximately 10% of the reproductive-aged women and this rate increases up to 50% among infertile women (1). Chronic pelvic pain, dysmenorrhea, dysparonia, and infertility are mostly encountered symptoms in these women.

Although the underlying mechanism has not been well understood, the most widely accepted theory is the retrograde menstruation as Sampson's theory. The shed endometrial cells into the peritoneal cavity through the Fallopian tubes have the property of adherence to peritoneum, proliferation, differentiation and penetration. Retrograde menstruation is encountered in 70-90% of the women. However, the prevalance of endometriosis is not so high. The reason for this can be explained by the differences in immunologic responses between women. The pathophysiologic process can be understood by the inability of immunologic system to remove shed endometrial cells as in tumoral development. There is increasing evidence supporting the alterations in both cell-mediated and humoral immunityin the pathogenesis of endometriosis. Increased number and activation of peritoneal macrophages, altered T cell and natural killer cell cytotoxicities in cellular immunity result in inadequate removal of ectopic endometrial cells from the peritoneal cavity. Another interesting point in the pathogenesis of endometriosis is inherent resistance of the ectopic endometrial cells against immune cells. It is also associated with the presence of autoantibodies, other autoimmune diseaes such as systemic lupus erytematosus, and recurrent abortion. Therefore endometriosis has been considered to be an autoimmune disease (2).

Programmed cell death 1 (PD-1) is a transmembrane protein expressed on T cells, B cells, and natural killer cells. It binds to the PD-1 ligand (PD-L1) and PD-L2. PD-L1 is expressed on the surface of multiple tissue types, including many tumor cells and hematopoietic cells. The PD-1 and PD-L1/2 interaction inhibits apoptosis of the tumor cell promoting peripheral T effector cell exhaustion. Based on several Phase II and III trials, antibodies inhibiting PD-1 and PD-L1 have been approved for multiple cancers such as renal cell carcinoma and melanoma (3).

We aimed to evaluate whether there is an expression of PD-L1 in the cell lining of endometrioma. Endometrioma may benefit from the effective use of antibodies against PD-L1 upon detection of expression of PD-L1.





Characteristics	Patients without PD-L1 stain	Patients with PD-L1 stain	P
Age	31±7.1	35.8±7.0	0.047
Cyst size (mm)	6.6±2.1	8.5±3.9	NS

Methods

The pathological specimens of 36 patients underwent surgery for endometriomas between May 2014 and May 2016 were stained by PD-L1 in this cohort study. Clinical and demographic characteristics including age, gravida, parity, the complaint of the patient on admission, cyst size, serum cancer antigen-125 (CA125) level, surgical characteristics such as the operation route, the presence of adhesion, laterality of the endometrioma, postoperative medication were obtained from the patients' medical records. Our hospital's Ethics Committee (Istanbul, Turkey) approved our study which was in accordance with the Declaration of Helsinki (diary number 2018-1/2). The trial was registered with ClinicalTrials.gov, number NCT03464799. The samples were prepared for routine tissue examinations. 2-3 micro-sized sections were taken from these paraffine-samples and examined with routine Hematoxylin and Eosin stain and PD-L1 immunohistochemical stain. The sections were scored for intensity as follows: absent (0), faint (1+), moderate (2+), intense (3+) and very intense (4+).

Results and Conclusions

The mean maternal age was 33.6 ± 7.4 years. There is no statistically significant difference between the recurrent and non-recurrent groups in terms of the immunohistochemical staining. The immunohistochemical staining for PD-L1 expression in endometriotic tissues was present in 52.8% of the patients (Figures).

The effective use of antibodies against PD-L1 upon detection of expression of PD-L1 in patients with endometriosis suggest that endometrioma may benefit from the use of these antibodies. Further researches are needed for a more detailed investigation.

References

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3- Kim J, Kim S, Lee HS, Yang W, Cho H, Chay DB, Cho SJ, Hong S, Kim JH. Prognostic implication of PD-1 protein and its ligand expressions in endometrial cancer. Gynecol Oncol. 2018;149(2):381-7.