Discovery of Programmed Death Ligand-1 (PDL-1) Expression in Central Nervous System Germinomas

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Introduction

Immunomodulation and tumor induced tolerance is one of the central mechanisms in the oncogenesis of malignant and benign neoplasms. While numerous pathways have been described, signaling through the Programmed Death 1 receptor (PD-1) on T lymphocytes, via activation through its ligand, Programmed Death Ligand 1 (PD-L1) is one of the central pathways involved in tumor induced tolerance. Germinomas of the central nervous system (CNS) have been classically characterized as a "Two Cell" tumor with histologic analysis exhibiting an abundance of quiescent tumor infiltrating lymphocytes. We therefore investigated whether PD-L1 expression may be responsible for germinoma induced T cell anergy, and if these tumors may be susceptible to immunotherapy.

Methods

Pathologic specimens obtained from 21 cases of CNS germinomas between 2000 and 2016 were analyzed for the presence of PD-L1 and PD1 expression by immunohistochemistry. 1.5mm core sections from each tumor was stained with antibodies directed toward PD-L1 (SP142, Ventana Benchmark; SP142, Leica Bond) and PD-1 (NAT105, Leica/Abcam). OCT3/4 staining was used to confirm germ cell tumor localization.

Results

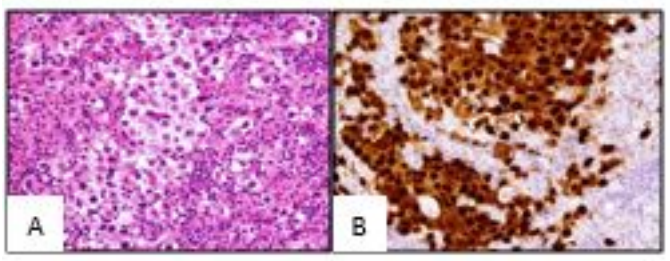
19 of 21 (90%) germinomas harbored germ cell components that stained positively for PD-L1. Positive lymphocyte staining for PD-L1 was evident in 16 cases. PD-1 expression was relegated to lymphocytes, as expected.

Table 1: Summary of IHC Results

Pt	Age/Sex	Location	PD-L1: tumor cells	PD-L1: lymphocyte	PD-1
1	13/M	Pineal	11-25%	blush	neg
2	24/F	Sella	6-10%	blush	neg
3	17/F	Sella	11-25%	blush	11-25%
4	19/M	Pineal	11-25%	blush	neg
5	24/M	Pineal	1-5%**	blush	neg
6	15/M	Ventricular	blush	negative	neg
7	21/M	Suprasellar	1-5%	blush	neg
8	34/M	Pineal	50%+	blush	neg
9	10/F	Suprasellar	11-25%	6-10%	neg
10	10/F	Sella	50%+	negative	6-10%
11	28/M	Stalk	50%+	negative	1-5%
12	13/F	Sella	6-10%	blush	1-5%
13	19/F	Suprasellar	6-10%	blush	1-5%
14	22/M	Tectum	26-50%	blush	1-5%
15	16/M	Pineal	50%+	blush	neg
16	15/M	Pineal	50%+	blush	neg
17	15/M	Pineal	6-10%	negative	neg
18	34/M	Pineal	50%+	negative	1-5%
19	34/M	Pineal	6-10%	blush	1-5%
20	19/M	Suprasellar	50%+	blush	1-5%
21	9/M	Pineal	negative	blush	1-5%

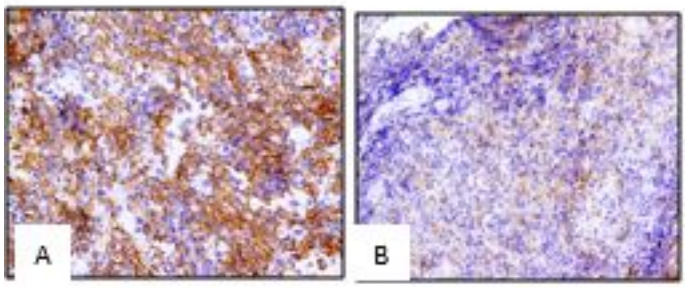
**Minimal tumor present in analyzed sample

Figure 1: Representative Histology/IHC



Photomicrographs (20x) depicting H&E (A) and Oct 3/4 (B) staining that was used to confirm the presence of germ cell tumor components in each core specimen analyzed.

Figure 2: Representative PD-L1 Expression



Representative PD-L1 expression in two different germinomas with high (greater than 50% PD-L1 expression, A) and faint PD-L1 expression (B). Photomicrographs at 20x

Conclusions

PD-L1 expression is detectable in the majority of sampled germinomas and may contribute to lymphocyte quiescence observed in these tumors. These results raise the possibility that immune checkpoint inhibitors may have a therapeutic role in future treatment of germinomas.

Learning Objectives

By the end of this session, participants should be able to:
1) Explain the mechanism of PD-L1 mediated tumor induced tolerance
2) Describe the histologic features of CNS germinomas
3) Describe how immune checkpoint inhibitors such as nivolumab may be useful in the treatment of CNS germinomas

References

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