Title

PD-1/PD-L1 expression in a series of intracranial germinoma and its association with Foxp3+ and CD8+ infiltrating lymphocytes

Abstract

Author(s)

Liu, Bin

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Kyoto University (京都大学)

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Kyoto University
Central nervous system (CNS) germ cell tumors are common in Asia, where they account for 8-15% of all CNS tumors of childhood, compared to 3-4% in the United States. In about 10-20% of patients, the tumor recurs 10 years after first-line treatment. Thus, alternative therapeutic strategies for treating refractory tumors have become the main goals of current pediatric oncological efforts. Programmed cell death 1 (PD-1) is a receptor in the CD28 family, and plays an important role in immune tolerance and immune escape for a variety of tumor cells. However, the expression of PD-1 and its ligand PD ligand 1 (PD-L1) in intracranial germinoma remain unknown. Furthermore, large tumor cells of intracranial germinoma are frequently accompanied by an abundance of tumor-infiltrating lymphocytes (TILs), which suggests that immune escape mechanisms are involved in tumor development. The current work aims to investigate the expression of PD-1/PD-L1 axis and subtypes of TILs in intracranial germinoma.

Expressions of PD-1 and PD-L1 were detected immunohistochemically in 25 formalin-fixed, paraffin-embedded tumor specimens from 24 patients with intracranial germinoma, consisting of 22 primary and 3 recurrent tumors. In 25 tumor tissues, including all recurrent samples, expression of PD-1 in TILs was identified in 96% and PD-L1 in tumor cells was identified in 92%. High expression of PD-1 in TILs and PD-L1 in tumor cells were detected in 76% and 88%, respectively. In addition, PD-1 expression was not related to PD-L1 expression in the current cohort.

To evaluate subtypes of TILs, quantification of lymphocytes with CD3, CD8, CD4, and Foxp3 expression was performed. Widespread TILs of variable density with perivascular and dispersed foci were identified in intracranial germinomas. Among TIL subtypes, Foxp3+ TIL density was associated with CD3+, CD4+, and CD8+ TIL density, respectively. CD4+ TIL density correlated with CD8+ TIL density.

Associations between expression of PD-1 or PD-L1 and TIL subtype densities were evaluated. In 22 initial germinoma cases, CD3+ TIL density was significantly higher among patients with high expression of PD-1 than in those with low expression of PD-1. Higher Foxp3+ density and higher CD8+ TIL density in patients with high expression of PD-1 than in those with low expression of PD-1. However, no significant difference in CD4+ TIL density was evident between patients with high and low expressions of PD-1. Furthermore, Foxp3+/CD4+ ratio was higher in patients with high expression of PD-1 than in those with low expression of PD-1.