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The analysis of tumor infiltrative lymphocytes in corticotroph adenomas and its relation to hormonal status

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Background: Corticotrophs are a well-known tissue susceptible to cytotoxicity by lymphocytes, as seen in autoimmune hypophysitis, suggesting that immunological approach may be one of the therapeutic strategies for ACTH-producing

adenomas. However, the efficacy of immune therapy for general ACTH-producing adenomas remains unclear. And cortisol levels expected to affect the tumor microenvironment (TME). **Objectives:** To clarify whether ACTH-producing adenomas are sensitive to immunotherapy and if this approach can be a potential treatment for these challenging tumors. **Methods:** TME was examined by immunostaining using pituitary adenomas specimens. This study consists of two phases: In phase 1, TME of ACTH-producing adenomas (n=29) was analyzed by comparing with GH-producing pituitary adenomas (GHomas) (n=10) and nonfunctioning pituitary adenomas (NPAs) derived from gonadotrophs origin (Gnomas) (n=10). In phase 2, corticotroph adenomas were divided into three groups that were considered to be at different cortisol exposure; naïve ACTH-producing adenomas (Naïve, n=29), treatment with metyrapone (Met, n=13), and silent corticotroph adenomas (SCAs) (n=12). These TME were analyzed and compared. To detect T-lymphocytes and M2 macrophages, antibodies to CD3, 4, or 8, and CD163 were used, respectively. The association between TME and patients' background data including urinary free cortisol levels were analyzed. **Results:** Phase 1: Tumor infiltrating lymphocytes (TILs) evaluated by CD3 + cells inACTH-producing adenomas were less than those in the GHomas (p<0. 01) and lower tendency compare to Gnomas (p=0. 05). Among them, CD8 + cells in ACTH-producing adenomas were less than both (p<0. 01, p<0. 01, respectively). CD163 + cells were widely distributed in ACTH-producing adenomas but less than Gnomas (p<0. 01). The number of CD163 + cells were not associated with tumor aggressiveness or invasiveness in ACTH-producing adenomas. Phase 2: First, SCAs, NPAs from corticotroph origin were compared to Gnomas, showing that less CD8 + cells were detected in SCAs (p<0. 01), suggesting low CD8 + cells were common feature of corticotroph adenomas regardless of cortisol level. Among 3 groups of different cortisol exposure, CD4 + cells were higher both in Met and SCAs than in Naïve (p<0. 01, p=0. 01, respectively), while CD8+ cells were not altered. In contrast, the number of CD163+ cells were lower in Met than Naïve (p<0. 01), suggesting the association between cortisol levels and the number of CD163 + cells. **Conclusions:** We revealed for the first time that low TILs are common features among corticotroph adenomas regardless cortisol levels. Moreover, the CD4 + cells but not CD8 + cells were higher in tumors with low cortisol status, suggesting induction of CD8 + cells are required for the immune therapy to corticotroph adenomas. Regarding with CD163 + cells, no association with tumor behavior was shown rather related to cortisol exposure status.

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