

## Parathyroid Carcinoma has a PD-L1 Expression, and Share with Atypical Neoplasms an Abundant Intratumoral Macrophagic Infiltration - A Short Commentary

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### Abstract

**Background:** In the era of immunotherapy as a therapeutic option for solid tumors, the immuno-tumor characterization of parathyroid neoplasms is timely and necessary. Since conventional therapeutic options are limited for controlling the progression of parathyroid carcinoma, new modalities of treatment are desperately needed. Four distinct tumor microenvironments have been proposed based on the existence of tumor-infiltrating lymphocytes (TILs) and programmed death-ligand 1 (PD-L1); type I (TILs+/PD-L1+), type II (TILs-/PD-L-), type III (TILs-/PD-L1+), and type IV (TILs+/PD-L1-). These immunogenic subtypes may predict responses to these therapies.

**Aim:** The aim of this study was characterized programmed death-ligand 1 (PD-L1) expression and tumoral-infiltrating lymphocytes (TILs) in parathyroid carcinoma (PC) and atypical parathyroid neoplasms (ANs).

**Methods:** Our tissue samples constitute 30 parathyroid tumors (17 PC and 13 ANs) which were available from a prospectively collected database at the University of Texas M.D Anderson Cancer Center from 1996 to 2016. All samples were meticulously reviewed utilizing the current World Health Organization histopathological criteria. Each of the samples was immunohistochemically analysed for PD-L1, CD3, CD8 and CD68 with an automated staining system (BOND-MAX, Leica Biosystems, Buffalo Grove, IL). The Novocastra Bond Polymer Refine Detection Kit (Leica Biosystems) was used to detect PD-L1, CD3, CD8, and CD68 expression in tumor cells. Digital image analysis was performed using Aperio software (Leica Biosystems); PD-L1 expression was analysed with a tumor membrane-specific algorithm, CD3 and CD8 expression with a tumor nuclear staining algorithm, and CD68 expression was evaluated with a tumor cytoplasmic staining algorithm. The PD-L1 H score was calculated using the formula  $(1 \times (\% \text{ cells } 1+)) + (2 \times (\% \text{ cells } 2+)) + (3 \times (\% \text{ cells } 3+))$  and the other immunomarkers were calculated in accordance with the number of TILs positive by mm<sup>2</sup> of the parathyroid tumor. For the immuno-classification of the PC in this study, a PD-L1  $\geq 1$  was used as a cut-off for positivity. High expression of TILs was defined as cases with CD3+ and CD8+ density higher than that in the median PC group.

**Results:** The analysis of the immuno-data showed no difference in the median of PD-L1 H score between PC and ANs. All locoregional recurrences (n=6), distant metastases (n=5), and deaths due to disease (n=3) occurred in the PC group. We found four cases with a PD-L1 H score  $\geq 1$  associated with high expression of CD3+ (median 59.9 (27.4-986.8) cells/mm<sup>2</sup>), CD8+ (median=50.6 (4.5-1107.1) cells/mm<sup>2</sup>), and CD68+ (median 221.7 (53.0-741.1) cells/mm<sup>2</sup>) tumor cell density, and two had distant metastases (lung and liver). We identified 9 PC with a median CD68 tumor cell density >194 cells/mm<sup>2</sup>, and four in this PC group developed locoregional recurrences with or without distant metastases. We immuno-classify PC based on the four immunotypes. 13 PC cases were in the immunotype with PD-L1 negative and 4 PC cases had PD-L1 H score  $\geq 1$  with or without TILs positive.

**Conclusions:** PCs tend to display immune tolerance tumor microenvironment (type IV). Additionally, 18% (3) of PCs had patterns of PD-L1 and TILs expression in their microenvironment (type I) suggesting a potential benefit from immunotherapy. Thus, tumor microenvironment profiling could be useful to identify PC cases that could benefit from immunotherapy, and additional investigation is warranted.

**Keywords:** Immunotherapy; Tumor-infiltrating lymphocytes

### Commentary

Current primary treatment of both primary and recurrent parathyroid carcinoma (PC) is limited to surgical resection; both

chemotherapy and radiotherapy have limited efficacy [1]. In recent years, there is a growing interest in the use of immunotherapy in different types of solid tumors, and whose indication is determined by the immunogenic biomarker expression in the tumor microenvironment [2]. Therefore, the immunohistochemical

determination of these immunomarkers is available for use in cancer centers in research and clinical practice.

The current study is appropriately focused on evaluating the type of immunogenic tumor microenvironment in these two parathyroid tumors, never before analysed [3]. Even the predominant tumor microenvironments in the PC groups were PD-L1 H score <1 regardless of the presence of TILs, and non-anti-PD-L1 therapies should be considered. Recent analyses have considered that PD-L1 H score  $\geq 1$  is not the only factor to consider for the indication and evaluation of response to anti-PD-L1 therapy. In fact, the validated determination of the cut-off point for the indication of anti-PD-L1 therapy has not been standardized, because solid tumors considered negative (PD-L1 <1) when were subjected to anti-PD-L1 therapy have presented a total response rate in at least 21% of cases [4]. We propose that prospective studies in large case cohorts are necessary to determine the precise cut-off point to predict response to anti-PD-L1 therapies and also identify the associated predictive markers or genetic mutational signatures responsible for the response or resistance to the anti-PD-L1 therapy. Additionally, we identified that PCs and ANs had abundant intratumoral macrophages (CD68 positive). This unique discovery could be an interesting focus of therapeutic interest in parathyroid cancer, for the evaluation of immunogenic cancer vaccines to modulate the presence of intratumoral macrophages and promote tumor

regression, which is currently being evaluated in other solid tumors with poor prognosis [5].

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