Immune infiltrate in malignant tumors treated with nivolumab and/or ipilimumab

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Introduction

The novel immune therapies with drugs against PD-1, PD-L1 and CTLA4 receptors (immune checkpoint inhibitor therapies) require a precise knowledge and characterization of the immune infiltrate. Recent studies could demonstrate that CD8+T-cells are an important indicator for the success of the treatment. As the human immune system is very complex, it is difficult to imagine that only one specialized subpopulation would be responsible for the effectiveness of a drug. Therefore in this study the different known components of the immune response in different areas of the malignant tumors were characterized by performing thorough immunohistological investigations. The aim of this study was to find out which specific immune infiltrate in different malignancies will be able to provide information regarding the success of immune checkpoint inhibitor therapies. Therefore not only the number and distribution of various T-cell-subsets but also of the B-cells, plasma cells, the macrophages as well as the PD-L1 status were analyzed and correlated to each other.

Patients, material and methods

Forty-two (42) cases of head and neck squamous cell carcinomas (HNSCC), 104 malignant melanomas (MM), and 50 non-small-cell lung cancers (NSCLC) were investigated by immunohistochemistry for CD3, CD4, CD8, T-BET, GATA3, FOXP3, CD20, IRF4, and PD-L1 expression. From few patients sequential samples at diagnosis and during/after therapy could be analyzed. The obtained findings were correlated with available survival data.

Results

The expression of PD-L1 in tumor cells (TCs) of HNSCC was similar in patients with progressive disease (PD), stable disease (SD) or partial response (PR), but differed regarding tumor-infiltrating lymphocytes (TIL's). Patients with SD or PR exhibited more PD-L1 positive TILs (30%) (Fig 1) than patients with PD (5%). In 9/42 cases TCs expressed GATA3 (Fig.2), in these cases the immune infiltrate contained significantly more T-BET (Fig.3) expressing T-cells than in the other cases.
In 70% of the MM the TCs expressed IRF4 (fFg.4) inducing a TH2 response, thus, most of these cases exhibited an immune infiltrate with features of TH2 response.
In contrast to all other investigated entities in NSCLC a stronger immune infiltrate of CD20 positive cells at the tumor invasion front was observed in 40 specimens (88.9%), indicating that the immune response in this tumor compartment is predominated by a B cell- rather than a T cell-response.
This phenomenon can be explained by the fact that the lungs additionally have direct contact with pathogens leading to an overlap of two immune reactions.

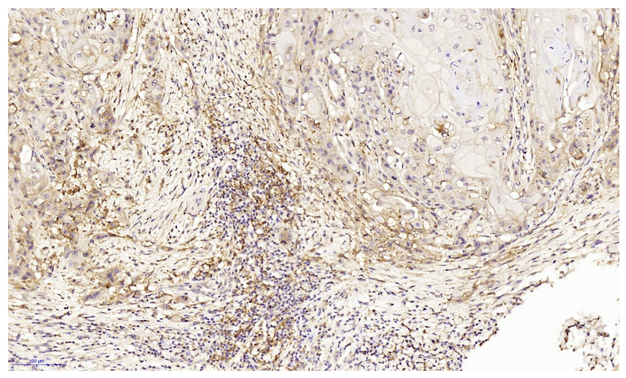

Fig.1 High PD-l1 expression in immune cells of a HNSCC from a patient with progressive desease

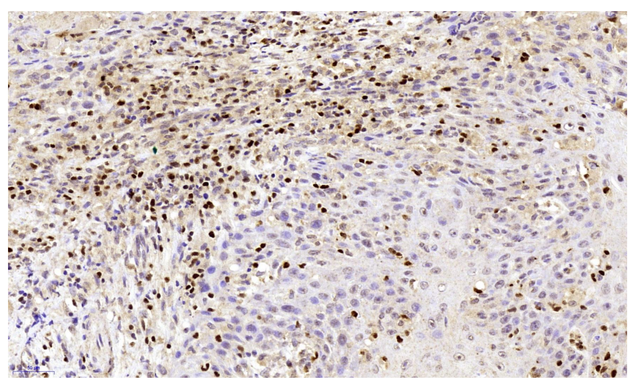

Fig. 2 T-BET expression in immune cells of a HNSCC-case characterized by GATA3 expression in tumor cells

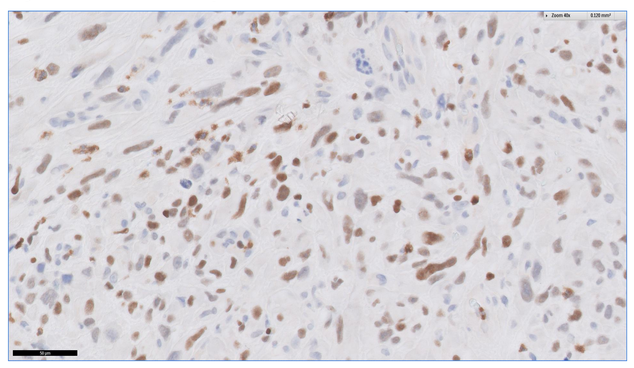

Fig. 3 GATA3 expression in tumor cells of a HNSCC

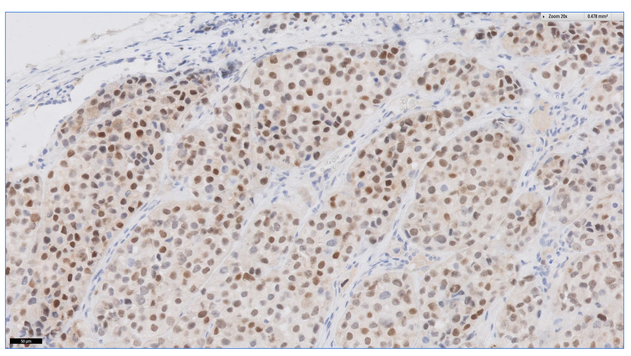

Fig. 4. MUM1/IRF4 expression in tumor cells of malignant melanoma

Conclusion

The composition of the immune infiltrate seems to be different in various tumor entities. This was obviously due not only to current therapy or previously applied therapeutic regimens, but also the type of tumor-bearing organs and their topography played an additional role with respect to the immune infiltrate .

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