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Introduction & Objectives: Testicular germ cell tumors (TGCTs) are naturally infiltrated by immune cells, especially seminomas (SEs). Thorough characterization of the immune infiltrate, immune checkpoint and mismatch repair protein (MMR) expression in these tumors has scarcely been reported in literature so far. We aim to assess the immunoexpression of PD-L1/CTLA-4 and of MLH1/PMS2/MSH2/MSH6 in a cohort of TGCTs, characterize the infiltrating immune cells and seek for clinicopathological correlates.

Materials & Methods: A total of 164 consecutively diagnosed patients (2005-2018) were included. Immunostaining (intensity and proportion of positive cells) was separately assessed both in immune cells (ICs) and tumor cells (TCs) and independently for each component of mixed tumors (reaching a total of 271 tumor samples). The type of immune infiltrate present in seminoma samples was further characterized (B/T-lymphocytes, NK cells, macrophages).

Results: Infiltrating ICs showed frequent immunoexpression of PD-L1 and CTLA-4 (in 83.5% and 96.3% of the cases, respectively); this prevalence of staining did not significantly differ among SE and non-seminoma (NS). Overall, patients with <20% CTLA-4-positive ICs showed significantly more *rete testis* invasion ($p=0.0232$) and those with absent PD-L1-positive ICs showed significantly more relapse ($p=0.0171$). Tumor cells exhibited immunoexpression of PD-L1 and CTLA-4 in 24.9% and 89.8% of the samples, respectively. Intensity of CTLA-4 staining in TCs was significantly higher in NS compared to SE ($p<0.0001$); specifically, it was significantly higher in teratomas, choriocarcinoma and yolk sac tumor components ($p<0.01$); TC immunoexpression of PD-L1 was significantly more frequent in choriocarcinomas and less frequent in teratomas ($p<0.05$). Lower combined immunoexpression scores for MLH1 and PMS2 were significantly more frequent in NS tumor samples ($p<0.0001$, $p=0.0001$). Teratomas and choriocarcinomas showed the lowest immunoexpression scores for all MMR proteins. Infiltrating T-lymphocytes in SEs were predominantly cytotoxic CD8+ T-lymphocytes, with 80.8% of the tumors showing a CD4/CD8 ratio <1. Lower T-lymphocyte and B-lymphocyte infiltration was significantly more common in pT2/3 SEs and stage III SEs when compared to pT1 ($p=0.0273$) and to stages I/II ($p=0.0401$), respectively. Lower B-lymphocyte proportion was also more common in SEs with *rete testis* invasion ($p=0.0071$).

Conclusions: PD-L1/CTLA-4 and MMR protein immunoexpression patterns in TGCTs differ among sub types and convey prognostic information. Given the frequent expression of immune checkpoints, immunotherapies might be of value in treatment of these patients, in selected clinical settings.